NOV 8 1944

Vol. 19 No. 99 September, 1944

Medical Library

ARCHIVES OF DISEASE IN CHILDHOOD

EDITORS
ALAN MONCRIEFF and RICHARD W. B. ELLIS

ASSISTANT EDITOR
A. WHITE FRANKLIN

EDITORIAL COMMITTEE

R. C. BROCK
H. C. CAMERON
H. A. T. FAIRBANK
LEONARD FINDLAY
G. B. FLEMING
CHARLES F. HARRIS
REGINALD MILLER
LEONARD G. PARSONS

EDITOR OF THE *British Medical Journal*

CONTENTS

PAGE

The treatment of coeliac disease with vitamin B complex and concentrated liver. DONALD PATERSON, MILA PIERCE AND ELEANOR PECK 99

Atrophic sclerosis of the cerebral cortex associated with birth injury. R. M. NORMAN ... 111

Prognosis and treatment of pneumonia in children. F. L. KING LEWIS 122

Observations on otitis media and mastoiditis in infancy. EDWARD C. ROSS COUPER ... 126

Case reports:

Congenital atresia of the oesophagus. J. N. O'REILLY, R. H. FRANKLIN AND M. D. DALEY 131

Giant congenital diverticula and neonatal rupture of colon. J. EDGAR MORISON ... 135

Imperforate anus. A. W. WILKINSON 138

Allergic vomiting in an infant. H. S. BRODRIBB 140

Two cases of pulmonary actinomycosis. A. G. WATKINS 143

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

YEARLY SUBSCRIPTION (4 NUMBERS) 25/- U.S.A. $6.00 SINGLE NUMBER 7/6

GENERAL ADVISORY BOARD.

F. M. B. Allen (Belfast).
H. T. Ashby (Manchester).
W. R. Bristow (London).
Alan Brown (Toronto).
E. Cautley (London).
Glen Davison (Newcastle-on-Tyne).
T. Y. Finlay (Edinburgh).
Sir John Fraser (Edinburgh).
W. E. Gallie (Toronto).
J. F. Gaskell (Cambridge).
G. R. Girdlestone (Oxford).
Sir Robert Hutchison, Bt. (London).
R. C. Jewesbury (London).
F. S. Langmead (London).
C. P. Lapage (Manchester).
Helen Mayo (N. Adelaide).
T. P. McMurray (Liverpool).
Charles McNeil (Edinburgh).
A. E. Naish (Sheffield).
C. Max Page (London).
D. H. Paterson (London).
W. J. Pearson (London).
T. G. Pugh (Carshalton).
F. C. Pybus (Newcastle-on-Tyne).
Sir Humphry Rolleston, Bt. (Haslemere).
J. D. Rolleston (London).
J. C. Spence (Newcastle-on-Tyne).
E. H. M. Stephens (Sydney).
G. Bruton Swiney (Auckland, N.Z.).
H. Thursfield (Basingstoke).
C. W. Vining (Leeds).
E. H. Williams (Dunedin, N.Z.).

NOTICE TO SUBSCRIBERS.

Subscriptions are payable to the British Medical Association. Address: British Medical Association House, Tavistock Square, London, W.C.1.

NOTICE TO CONTRIBUTORS.

All papers submitted for publication and all other editorial matters should be referred to Dr. Alan Moncrieff, Middlesex Hospital, London, W.1. Papers sent for publication should be typewritten. Illustrations will usually be inserted in the text itself, and care should be taken that the text is marked to show the desired position of each illustration. Charts and curves accompanying papers should be carefully drawn on tracing linen. Any lettering on these drawings should be lightly inserted in pencil.

References must be arranged according to the Harvard system. In the text the year of publication must follow the author's name, more than one paper in any one year being indicated by a small letter (a, b, c) after the date. No numbering of references is necessary. At the end of the contribution references are arranged in the alphabetical order of the authors' names. The reference details are then given as follows: Author's name, initials, year of publication (in brackets), title of periodical (in italics, abbreviated according to the *World List of Scientific Periodicals*), volume number (bold type, Arabic numerals) and page number (ordinary type, Arabic numerals). When a book is referred to, the place of publication, edition and page should be given. Further details of the system can be studied in the *British Medical Journal*, January 2nd, 1937, p. 33.

Contributors will receive one proof in page, but it is assumed that all but verbal corrections have been made in the original manuscript; an allowance at the rate of ten shillings per sheet of sixteen pages is made for alterations in the proof (printer's errors excepted), and contributors will be responsible for any excess.

Fifty free reprints of articles will be given, if desired, to contributors. Additional reprints at cost price can be supplied if application is made when returning proofs. An estimate of costs will be given if desired on application to the Publishing Manager, British Medical Association.

Papers which have been published become the property of the ARCHIVES and permission to republish must be obtained from the Editors.

THE TREATMENT OF COELIAC DISEASE WITH VITAMIN B COMPLEX AND CONCENTRATED LIVER

BY

DONALD PATERSON, M.D., F.R.C.P., MILA PIERCE, M.D., Capt. U.S. Army Medical Corps, and ELEANOR PECK, M.D., Lieut. U.S. Army Medical Corps

(From the Hospital for Sick Children, Great Ormond Street, London, W.C.1)

In his original clinical description of coeliac disease, to which little new can be added, Gee (1888) recorded that 'errors in the diet may occur,' but what errors? Whilst the essential cause is now known to be concerned with the defective absorption of both fats and carbohydrates, the explanation of this defect remains obscure. Certain aspects of the disease suggest that it may be a deficiency syndrome and that the vitamin B complex may be involved. The similarity of certain symptoms to those encountered in non-tropical sprue and in the chronic vitamin B deficiency syndrome of adults seems significant. The personality changes, the loss of strength and failure to grow, the gastro-intestinal symptoms, the reduced motility of the bowel, the bulky stools and the intolerance to fats and carbohydrates are common features of these three syndromes, all of which respond to the administration of crude liver extracts. The potent extracts contain members of the B complex, as well as the intrinsic haematopoietic factor, but which of the fractions or which combination of the complex brings about the improvement is undetermined.

Coeliac disease appears to be six or seven times more prevalent in the British Isles since the outbreak of war in September, 1939, as will be seen from the following figures:—

Period	No. of years	Total No. of new attend-ances at hospital *	Total No. of cases of true coeliac disease	Percentage of new hospital attend-ances which were coeliacs
Jan. 1924 to Dec. 1938.	15	445,074	73 (Hard-wick, 1939)	0·016
Sept. 1939 to Dec. 1943.	4½	67,501	76	0·113

War-time dietary arrangements. In order to make the dietary treatment of such children as easy as possible, the Ministry of Food arranged in 1942 that proved cases of coeliac disease, when certified as such by a physician, might receive additional rations of meat on surrender of their fat ration. In addition, in 1944 dried bananas were made available for such cases. Because of the problems related to the dietary treatment of coeliac disease under war-time conditions, the views of May et al. (1941) attracted much attention. They advocated a normal, balanced diet, supplemented by vitamins A, C and D, combined with the parenteral administration of crude liver and vitamin B complex. May claimed that this regime was superior to the more commonly accepted dietary treatment, which was a diet essentially low in fat and high in protein.

The purpose of this paper is to report our experiences over a period of one year (1943–44) and results to date, in cases of coeliac disease treated on a regime similar to that advocated by May et al.

1. Classification of types of cases

Thirty cases were studied and were classified as follows:—

	No. of cases
(*a*) Cases of idiopathic coeliac disease (table 1 and fig. 1) which were thoroughly investigated and met all the essential criteria, common to the idiopathic form of the disease	13
(*b*) Cases of idiopathic coeliac disease (table 2 and fig. 2) which presented the clinical picture, course and characteristic stool findings, but further confirmatory investigations were unobtainable due to war-time restrictions of laboratory services	13
(*c*) Cases in which a focus of infection was discovered during a period of observation—'coeliac syndrome' (table 3 and fig. 3)	4
	30

2. The criteria of diagnosis

(i) A history of refusal of food, failure to gain in height or weight, weakness and occasional vomiting.

(ii) Bulky, pale, offensive stools with intermittent bouts of looseness or constipation.

* Hospital for Sick Children, Great Ormond Street, W.C.1.

TABLE 1

Case		Age	Age at onset	Special clinical notes	Total stool fats				Blood		Vitamin A absorption curves peak rise, I.U.	Oral glucose tolerance curve peak rise, mgm. per cent.	X-ray barium meal	Pancreatic enzymes	Previous treatment
					Before treatment		After treatment		Hb. per cent.	R.B.C. millions per c.mm.					
					Date	per cent.	Date	per cent.							
1	J. D.	8 yr.	2½ yr.	Retarded growth: microcytic anaemia; osteoporosis	28.6.37	50·65	10.11.43	36·56	40	3·43	*B* not done *D* 24.2.44 no rise	*B* not done *D* 24.2.44—40			Low fat diet 4 years; campolon 1937
2	M. C.	6 yr.	5 yr.	Wasted; typical stools; microcytic anaemia	3.7.43	40·8	24.9.43 31.1.44	25·6 22·48	65	3·95	*B* 5.10.43 no rise *D* 10.12.43—8 *D* 12.5.44—33	*B* 5.11.43—5 *D* 9.5.44—40	+		None
3	K. T.	7 yr.	2½ yr.	Wasted; v. large abdomen; typical stools; microcytic anaemia	9.43	51·9	10.12.43	73·6	60	2·60	*B* 6.10.43—8 *D* 10.12.43—20 *D* 10.1.44—25	*B* 9.10.43—7 *D* 10.12.43—12	+		Low fat diet
4	M. T.	3 yr.	1½ yr.	Oedema; wasted; large abdomen; typical stools	22.8.43	50·7	8.2.44	26·1	75	4·40	*D* 27.12.43—no rise	*D* 21.12.43—40		Present	Low fat diet
5	G. D.	2 yr.	1½ yr.	Retarded growth; typical stools; breast fed 6 mth.	22.9.43	56·8	11.11.43	33	75	2·76		*B* 28.10.43—39 *D* 6.1.44—21	+	Present	None
6	D. S.	2 yr.	1 yr.	Late in walking; retarded growth; typical stools	27.9.43 Low fat diet	27·36	15.10.43	9·12	65	4·40	*B* 28.9.43—9·5 *D* 6.1.44—35	*B* 28.9.43—7 *D* 12.12.43—12	+	Present	Low fat diet
7	M. P.	3 yr.	1½ yr.	Wasted; retarded growth; breast fed 2½ mth.	17.8.43	58·16	25.1.44	38·08	70	4·40		*B* 18.9.43—no rise *D* 25.5.44—24			Low fat diet 6 mth.
8	D. M.	3 yr.	1 yr.	Wasted; retarded growth; breast fed 1 mth.	23.4.43	60·1	24.11.43	16·96	95		*B* 26.10.43—53 *D* 3.3.44—41	*B* 26.10.43—52 *D* 3.3.44—41	+		None

9	T. G.	3 yr.	2 yr.	Typical stool; large abdomen; breast fed 8 mth.	30.8.43	34·6	26.11.43	40·88	79		*B* 30.9.43—no rise *D* 26.2.44—no rise	*B* 30.9.43—no rise *D* 15.5.44—29	+		None
10	Y. F.	4 yr.	2½ yr.	Retarded growth; typical stools; breast fed 1 mth.	28.6.43	36·48	22.10.43 8.3.44	24·32 24·48	90	4·71	*B* 25.11.43—59 *D* 6.1.44—36	*B* 25.11.43—23 *D* 18.5.44—28	+		None
11	G. G.	2 yr.	1 yr.	Recurrent diarrhoea; breast fed 6 mth.	29.10.43	33·6	18.4.44 Low fat	24·6 diet	85	4·92	*B* 23.11.43—18	*B* 23.11.43—10			Pancreatic and liver extract orally since 14.6.43; low fat diet
12	J .M.	2 yr.	1 yr. 2 mth.	Wasted; recurrent remissions; large abdomen	3.3.43	36·6	13.10.43	46·48	74	3·83	*D* 6.1.44—no rise	*D* 6.1.44—18	+	Present	1942 Liver extract with rapid gain; low fat diet
13	R. A.	1 yr. 3 mth.	1 yr. 1 mth.	Wasted; large abdomen; typical stools	13.10.43	59·76	24.11.43	32·0			*B* 10.12.43—51	*B* 2.11.43—26 *D* 21.12.43—35	+	Present	None

B .. .. .. Before treatment.

D .. .. .. During treatment (see also tables 2 and 4).

(iii) A total stool fat (well split) above 30 per cent. of a three-day sample of dried faeces.

(iv) Children presenting the symptoms mentioned above were further investigated for:—

(a) foci of infection in the respiratory tract and sinuses;

(b) abnormalities of the gastro-intestinal tract; and

(c) signs of tuberculous and other infections.

(v) To differentiate the true idiopathic case from the secondary or infective 'coeliac syndrome' the following investigations were also carried out:—

(a) **The oral glucose tolerance curve** as a measure of glucose absorption. (The Folin-Wu method of estimation was used throughout this series and a peak rise of 40 mgm. per cent. or over was regarded as normal. Readings were taken at half-hourly intervals).

(b) **The vitamin A absorption curve** as a criteria of fat absorption (Breese and McCoord, 1939; Yudkin, 1941).
(NOTE.—The expected rise from the fasting level is 70 to 150 I.U. in 2 to 5 hours, after a test dose of 7000 I.U. of vitamin A per kgm. of body weight. Halibut-liver oil containing 44,000 I.U. per c.c. was used in this series.)

(c) **The barium meal** as a measure of motility of the small bowel (Snell, 1934). In cases of coeliac disease, there is a characteristic clumping of the barium and a loss of the normal feathering pattern of the small bowel.

(d) **The estimation of trypsin** in the aspirated duodenal contents to exclude fibro-cystic disease of the pancreas * (Andersen and Early, 1942).

3. Treatment

The following preparations were used:—

(1) Liver

PROETHRON FORTE (ARMOUR)—2 c.c. intramuscularly 2 to 3 times weekly (alternate days).

(2) Vitamin B complex

(i) PARENTERAL

(a) LEDERLE'S B COMPLEX—2 to 3½ c.c. intramuscularly 2 to 3 times weekly (alternate days).

FORMULA:		
Thiamine hydrochloride	3 mgm.	per c.c.
Nicotinamide	16 mgm.	
Riboflavin	0·3 mgm.	
Pyrodoxin	0·5 mgm.	
Pantothenic acid ..	1·7 mgm.	
Vitamin extract from 55 grammes of fresh liver		

(b) BEMINAL (Ayers, McKann & Harrison, Ltd.)—1·5 c.c. intramuscularly 2 to 3 times weekly (alternate days).

FORMULA:		
Thiamine hydrochloride	10 mgm.	per c.c.
Nicotinamide	25 mgm.	
Riboflavin	0·5 mgm.	
Pyrodoxin	0·5 mgm.	
Calcium pantothenate ..	0·5 mgm.	

(ii) ORAL

B-PLEX (JOHN WYETH)—8 to 16 c.c. by mouth daily.

FORMULA:		
Thiamine hydrochloride	0·125 mgm.	per c.c.
Nicotinic acid	0·625 mgm.	
Riboflavin	0·1 mgm.	
Pyrodoxin	0·05 mgm.	
Pantothenic acid ..	0·13 mgm.	

The injections were given either as an in-patient at the hospital or by the family doctor at home, under our direction.

(4) Diet

This varied in individual cases. A normal balanced diet throughout the whole period of treatment was aimed at. In the severe cases, however, this was found impracticable, because of the recurrence of diarrhoeal stools, and a low fat diet was therefore necessary for a limited period. After three to four weeks of treatment, however, it was found possible to introduce fats and a normal diet was well tolerated thereafter, except in a few cases which required restriction of cooked fats (e.g. bacon, pastry, fried foods), throughout the period of treatment. It is noteworthy that uncooked fats (e.g. milk and butter fat) were well tolerated by all the children after the first few weeks of treatment.

(5) Criteria of improvement following treatment

This was measured by—

(i) Gain in weight and height.

(ii) General improvement in appearance and temperament of the child and alteration in the character and fat content of the stools.

(iii) Repetition of the oral glucose tolerance curve and vitamin A absorption curve in order to show whether an improvement in carbohydrate and fat metabolism had occurred.

An analysis of the 30 cases investigated is given in tables 1, 2 and 3.

Group A

Table I summarizes the clinical and diagnostic data on the 13 well-investigated cases of the idiopathic type.

(i) PREVIOUS TREATMENT. All but one case (1, J. D.) were new patients during 1943; six were previously untreated; seven had been controlled by low fat diets, of whom three had also received short courses of liver extract parenterally or orally.

(ii) ONSET. The onset of the disease was under 2 years of age in eight cases, at about 2½ years in four cases and at 5 years in one case.

(iii) CLINICAL PICTURE. This was characteristic in all cases.

(iv) TOTAL STOOL FATS. In twelve cases these were above 30 per cent. in a three-day sample of dried

* This term is open to certain objections. Andersen, in the article quoted, refers to 'congenital pancreatic deficiency' which is to be preferred. Other terms used are 'fibrosis of pancreas' and 'cystic fibrosis of pancreas'.—EDITORS.

faeces collected while the child was on a normal diet for his or her age. The remaining case (6, D. S.) was on a low fat diet when the fat estimation on the stool was made

(v) VITAMIN A ABSORPTION CURVES. These were obtained before treatment in seven cases and either before or during treatment in eleven cases. In the cases investigated before treatment, flat curves were obtained in three of the seven cases and peak rises of 18 I.U. (11, G. G.), 51 I.U. (13, R. A.), 53 I.U. (8, D. M.), and 59 I.U. (10, Y. F.) in the remaining four cases.

(vi) ORAL GLUCOSE TOLERANCE CURVES. Curves were recorded in ten cases before treatment. Of these nine were considerably less than 40 mgm. per cent. The remaining case (8, D. M.) showed a late rise of 52 mgm. per cent. at 90 minutes; this was possibly due to the child's struggling.

(vii) X-RAYS FOLLOWING A BARIUM MEAL. A barium meal was given and x-rays were obtained in nine cases, all of which were characteristic of coeliac disease.

(viii) DUODENAL JUICES. In five of the cases these were tested for trypsin; all were found to be normal.

Duration of treatment. The children of this group received from 4 to 6 c.c. of the liver concentrate and 6 to 10 c.c. of the vitamin B complex intramuscularly per week. The preparations were given in rotation, Sunday usually being omitted (see fig. 1).

Response to treatment

(i) DIET AND GAINS IN WEIGHT. The weight gains are recorded in fig. 1. No weight records were available before treatment was instituted. The gains during the first two months were 3 lb. or more in five cases and more than 1 lb. in all but one of the remaining eight cases.

Gains were slow and somewhat erratic during the first three months in five cases, after which they improved steadily. Cases 11 (G. G.), 5 (G. D.) and 4 (M. T.) were particularly slow in gaining and required restriction of their fat intake during the early weeks of treatment.

(ii) TOTAL STOOL FATS. This returned to the normal level (30 per cent. or less of the dried stool) in six cases. In three cases (3, K. T.; 9, T. G.; and 12, J. M.) the total fat content remained as high as before therapy was instituted, after periods of treatment of three, three and seven months, respectively. There was improvement in the fat content in the remaining ten cases.

(iii) VITAMIN A ABSORPTION CURVE. Fat absorption as measured by this curve was recorded in five cases, both before and during treatment. None returned to normal. (See table 4 for peak rises after therapy was instituted.) In cases 2 (M. C.), 3 (K. T.) and 6 (D. S.) there was an appreciable improvement in the peak rise after 2 to 3 months of treatment. In cases 8 (D. M.) and 10 (Y. F.) the levels were unimproved. In case 1 (J. D.), although one estimation only was obtained, namely, after one year of treatment, no absorption of the vitamin occurred. It is worthy of note that this flat curve was recorded although clinical improvement was marked and an oral glucose tolerance curve, estimated at the same time, was quite normal.

(iv) ORAL GLUCOSE TOLERANCE CURVES. These

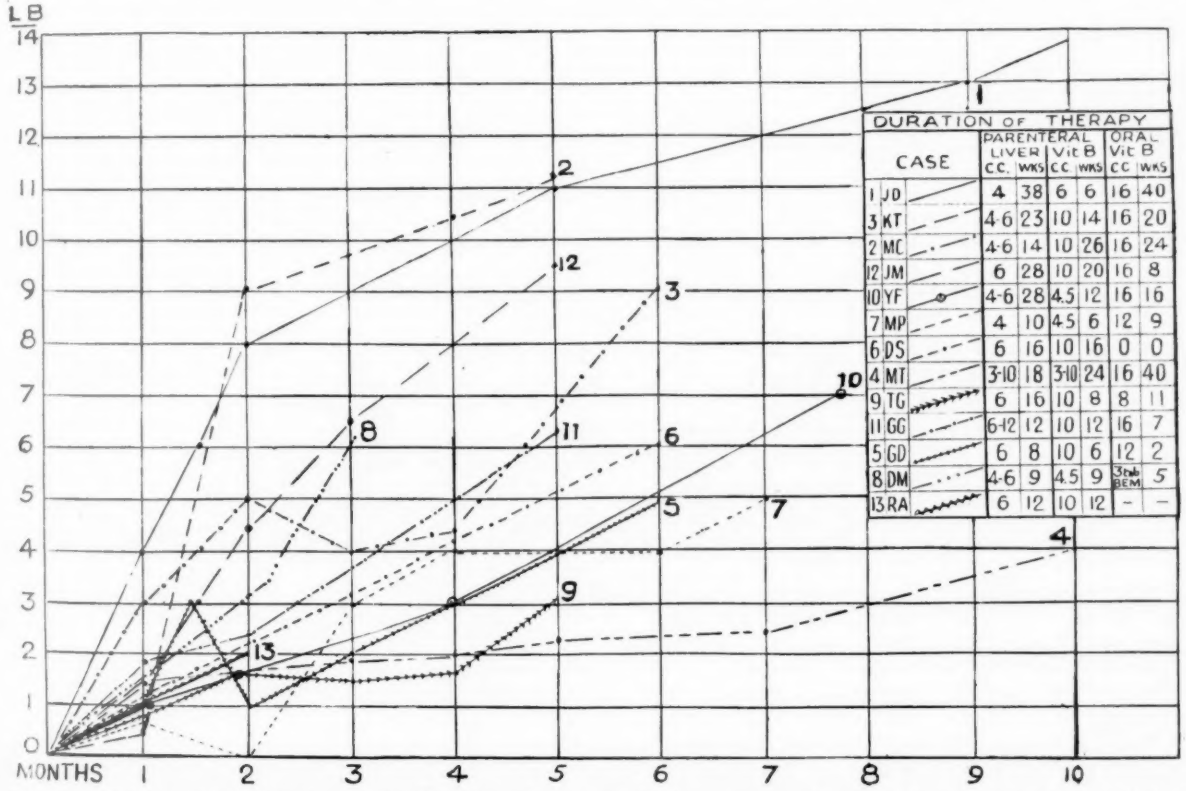


FIG. 1.—Weight gains in relation to the duration of therapy of thirteen cases of coeliac disease, treated intensively.

TABLE 2

Case		Age	Age at onset	Special clinical notes	Total stool fats				Blood		Vitamin A absorption curve peak rise I.U.	Oral glucose tolerance curve peak rise mgm. per cent.	X-ray barium meal	Pancreatic enzymes	Previous treatment
					Before treatment		After treatment		Hb. per cent.	R.B.C. millions per c.mm.					
					Date	per cent.	Date	per cent.							
14	P. K.	2½ yr.	9 mth.	Protuberant abdomen; typical stools	5.4.43	66·8	5.7.43	25·18	65	4·30					None
15	J. R.	1½ yr.	9 mth.	Anorexia; typical stools; failure to gain	22.2.43	46·8	16.6.43	18·08	80	4·00					None
16	B. F.	3 yr.	11 mth.	Large abdomen; wasted; microcytic anaemia; breast fed 1 wk.	21.6.43	16	16.11.43	36·92	55	3·74					Low fat diet
17	M. B.	3¼ yr.	9 mth.	Protuberant abdomen; typical stools; twin	29.9.41	61·54	28.4.43	12·85 L.F.	—	—					Low fat diet, Sept. 1941 to March 1943
18	S. W.	2½ yr.	1½ yr.	Large abdomen; wasted buttocks; typical stool	13.3.43	51·9	30.4.43	28·2	70	—					None
19	M. G.	3½ yr.	2 yr.	ditto	22.2.43	67·5	28.7.43	8·4	—	—					None
20	P. B.	2 yr.	1 yr.2 mth.	ditto	10.3.43	44	1.5.44	30·2	60	—					Low fat
21	P. Mc.	3 yr.	1 yr. 10 mth.	Anorexia; large abdomen; typical stools	14.9.43	50·4	10.11.43 24.2.44	20·80 28·88	50	3·79	*D* 25.2.44—67	*B* 30.11.43—31	+		None
22	M. H.	5 yr.	3 yr.	Wasted; protuberant abdomen; typical stools	30.5.43	48·16	2.11.43 12.5.44	38·24 24·88	60	4·5		*D* 4.5.44—25	+		Liver therapy
23	C. S.	6 yr.	5 yr.	Underweight; protuberant abdomen; typical stools	23.11.42	37·4	26.11.43	20·24	70	5·0		*D* 9.12.43—9			Low fat diet and liver therapy
24	E. B.	8 yr.	2 yr. 9 mth.	Stunted; microcytic anaemia	1.2.42	56·96	12.11.43	17·60	60	3·80	*D* 15.12.43—48·5 *D* 24.3.44—29	*D* 7.12.43—52 *D* 14.3.44—62		Present	None
25	F. S.	2 yr.	1 yr. 8 mth.	Typical stools; anorexia; microcytic anaemia	22.2.43	52·8	7.1.44	16·88	70	3·88		*B* 24.2.43—30			None
26	A. S.	2¾ yr.	1½ yr.	Moderate wasting; large abdomen; typical stools	12.12.43	37·28	8.11.43	8·48	—	—					None

were made on nine cases both before and during treatment. Two cases were found to have a normal peak rise of 40 mgm. per cent. or over, after treatment. Improvement was shown in seven cases.

Group B

Table 2 summarizes the clinical and diagnostic data on thirteen cases of the idiopathic disease which were less fully investigated. The essential differences between the group of cases in tables 1 and 2 are:—

(a) the thoroughness with which they were investigated, and

(b) the intensity of treatment.

They are discussed separately, not because the clinical features differed, but because this division simplifies the evaluation of therapy.

(i) PREVIOUS TREATMENT. Of the thirteen cases, eight had not been treated previously; four had had their intake of fats restricted; two had received short courses of liver parenterally.

(ii) ONSET. The age of onset was two years or under in ten cases and between two and five years in three cases.

(iii) CLINICAL PICTURE. This, together with the history, was characteristic in all cases.

(iv) TOTAL STOOL FATS. In all cases these were above 30 per cent.

(v) VITAMIN A ABSORPTION CURVES. These were obtained in only two of the thirteen cases and were assessed some little time after therapy was instituted.

(vi) ORAL GLUCOSE TOLERANCE CURVES. Blood sugar curves were obtained before therapy in only two cases, the peak rises being less than 40 mgm. per cent.

(vii) X-RAY FOLLOWING A BARIUM MEAL. A barium meal followed by x-rays was given in two cases; both films showed a characteristic result.

(viii) DUODENAL JUICE. This was obtained from only one case (24, E. B.) and was quite normal as regards trypsin content.

Duration of treatment. Nine of the thirteen cases received both liver and vitamin B complex parenterally. The remaining four received liver parenterally, but the vitamin B complex was given orally.

Response to treatment

(i) DIET AND GAINS IN WEIGHT. Weight gains in this group were less rapid than in the majority of cases shown in fig. 1. A closer analysis of the intensity and duration of treatment may explain this difference (see fig. 2).

The weight gains of the four cases 21 (P. Mc.), 26 (A. S.), 17 (M. B.) and 24 (E. B.), who were given B complex orally are particularly interesting. They gained slowly, but steadily, and there were no exacerbations in their symptoms. They were able to tolerate diets containing butter fat and lard and by restricting cooked fats (e.g. bacon fat, fried foods) and encouraging the use of vegetable protein, diets could be managed without special rationing. Since the clinical progress was satisfactory, intensive therapy was not instituted.

(ii) TOTAL STOOL FATS. After varying periods of treatment, analysis of the stool fats was repeated, and in twelve of the thirteen cases the total fat content was within normal limits. In the thirteenth case (16, B. F.) it remained at 36·92 per cent.

(iii) VITAMIN A ABSORPTION CURVES. These were obtained in cases 21 (P. Mc.) and 24 (E. B.) after three and four months of treatment respectively. The peak rises were 67 I.U. (21, P. Mc.) and in case 24 (E. B.) two curves were obtained—48 I.U. and 29 I.U.

(iv) ORAL GLUCOSE TOLERANCE CURVES. In none of the cases was a glucose curve obtained before and after therapy.

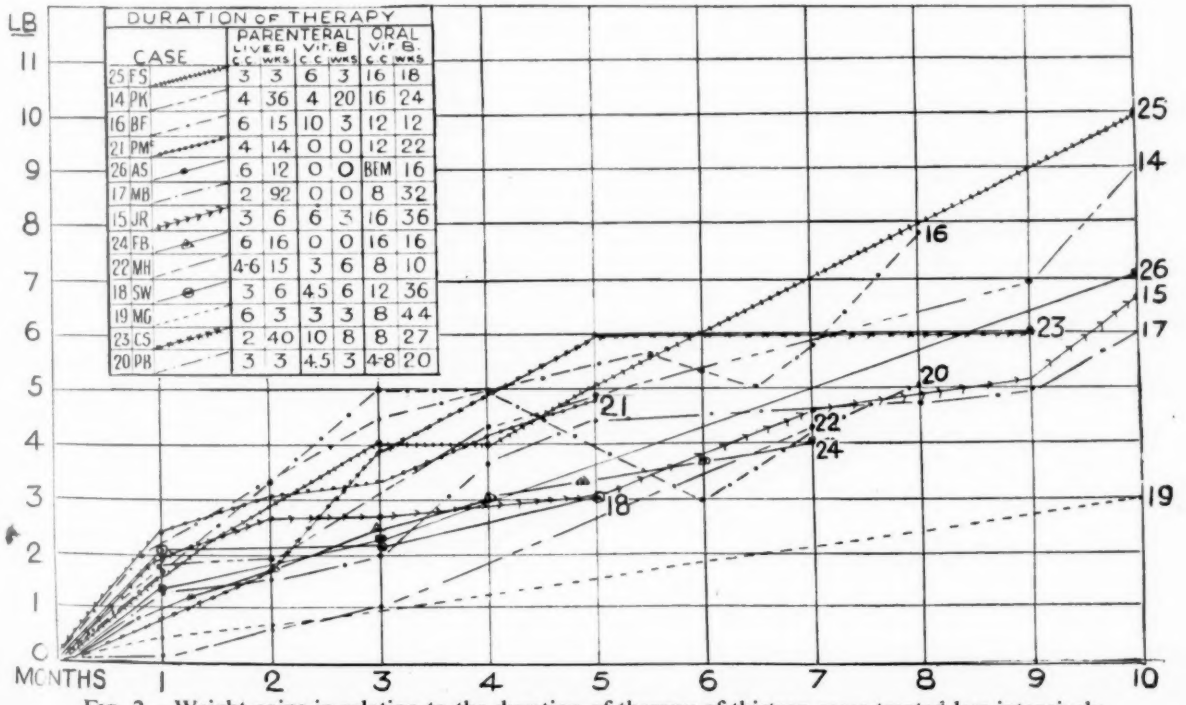


FIG. 2.—Weight gains in relation to the duration of therapy of thirteen cases treated less intensively.

TABLE 3

Case		Age	Age at onset	Special clinical notes	Total stool fats				Blood		Vitamin A absorption peak rise, I.U. date	Oral glucose tolerance curve peak rise, mgm. per cent.	X-ray clumping small bowel	Trypsin	Previous treatment
					Before treatment		After treatment		Hb. per cent.	R.B.C. millions per c.mm.					
					Date	per cent.	Date	per cent.							
27	B. H.	2 yr.	1 yr.	Stunted; typical stools: repeated U.R.I.*	6.10.43	45·5	24.11.43	22·8	65	4·04	19.11.44—7	19.11.44—133	—	—	None
28	C. T.	1 yr. 7 mth.	1 yr. 2 mth.	Stationary weight; typical stools; prominent abdomen; Sonne, Nov. 43	27.4.43	7·8	6.5.43	13·8	65	4·32		13.12.43—21	—	—	Low fat diet
29	A. B.	10 yr.	2 yr.	Typical stools; repeated U.R.I.	1941	48·5	27.1.44	36·8	79	4·29	10.1.44—18	11.12.43—89	+	+	Campolon
30	J. J.	2 yr.	1 yr.	Fragile; marked anorexia; repeated U.R.I.	Diarrhoeal stool no fat estimation		10.3.44	40·8	69	5·3	20.1.44—7	20·1·44—41	not definite	+	None

* U.R.I.=Upper respiratory tract infection.

TABLE 4

VITAMIN A ABSORPTION LEVELS AND ORAL GLUCOSE TOLERANCE CURVE LEVELS (before and after treatment

Case		Vitamin A				Latest stool fats		Oral glucose tolerance			
		Date	Fasting levels		Peak rise, I.U.	Date	per cent.	Date	Fasting level, mgm. per cent.	Maximum rise, mgm. per cent.	Peak rise, mgm. per cent.
			Carotenoids I.U.	Vitamin A I.U.							
1*	J. D.	*B* — *D* 24.2.44	69	45	−7	10.11.43	36·5	*B* — *D* 24.2.44	0·120	0·160	40
2	M. C.	*B* 5.10.43 *D* 10.12.43 *D* 12.5.44	19·5 26 56	83 97 45	0 8 33	 1.11.43 31.1.44	 25·6 22·4	*B* 5.11.43 *D* 9.5.44	0·080 0·107	0·085 0·147	5 40
3	K. T.	*B* 6.10.43 *D* 10.1.44	29 38	60 60	8 25	 20.12.43	 73·0	*B* 9.10.43 *D* 10.12.43	0·095 0·116	0·102 ·0128	7 12
5	G. D.	No estimation made				11.11.43	33·0	*B* 28.10.43 *D* 6.1.44	0·070 0·073	0·109 0·094	39 21
6	D. S.	*B* 28.9.43 *D* 6.1.44	56 44	33 73	9 35	 15.10.43	 9·12	*B* 28.9.43 *D* 12.12.43	0·095 0·116	0·102 0·128	7 12
7	M. P.	No estimation made				25.1.44	38·0	*B* 18.9.43 *D* 25.5.44	0·104 0·112	0·104 0·136	0 24
8	D. M.	*B* 26.10.43 *D* 3.3.44	38 38	36 79	53 41	26.11.43	16·9	*B* 26.10.43 *D* 3.3.44	0·177 0·106	0·129 0·147	52 41
9	T. G.	*B* — *D* 26.2.44	72	62	0	24.11.43	48·7	*B* 30.9.43 *D* 15.5.44	0·119 0·098	0·112 0·129	−7 29
10	Y. F.	*B* 25.11.43 *D* 6.1.44	32 43	103 73	59 36	8.3.44	24·8	*B* 25.11.43 *D* 18.5.44	0·073 0·068	0·096 0·096	23 28
13	R. A.	*B* 10.12.43	38	76	51	24.11.43	32·0	*B* 2.11.43 *D* 21.12.43	0·086 0·065	0·109 0·100	23 35

* Not estimated before treatment, but referred to on page 103 as of special significance.

Group C

Four cases which presented the physical appearance and stool characteristics of the coeliac syndrome were separated from the idiopathic group by findings indicative of a chronic focus of infection of etiological significance. Table 3 and fig. 3 summarize the essential features and response to treatment in these cases.

(i) CLINICAL PICTURE. This was suggestive in all four cases, but the evidence of chronic sinus and upper respiratory infection in cases B. H., A. B. and J. J. and Sonne dysentery in C. T. made the diagnosis of coeliac disease questionable.

(ii) TOTAL STOOL FATS. This was above 30 per cent. in all four cases.

(iii) VITAMIN A ABSORPTION CURVE. The peak rise was low in the three cases tested, namely, 7 I.U. (B. H.), 18 I.U. (A. B.) and 7 I.U. (J. J.).

(iv) THE ORAL GLUCOSE TOLERANCE CURVE. The values were normal in three of the four cases, peak rises being obtained as follows: 133 mgm. per cent. (B. H.), 89 mgm. per cent. (A. B.) and 41 mgm. per cent. (J. J.). The rise in the other case (C. T.) was 21 mgm. per cent. only.

(v) X-RAYS FOLLOWING A BARIUM MEAL. These showed clumping of the barium in one case, namely, A. B.

(vi) DUODENAL JUICE. The history of repeated upper respiratory infections together with a low vitamin A absorption curve, suggested the possibility of fibro-cystic disease of the pancreas in cases B. H., J. J. and A. B. Analysis of the duodenal juice was found to be normal in all three cases.

The occurrence of upper respiratory infections is not an uncommon feature of children with idiopathic coeliac disease. Chronic sinusitis and recurrent pulmonary infections appear to be causative factors of the ' coeliac syndrome ' rather than the result of previously existing idiopathic coeliac disease. Similarly, chronic infections of the gastro-intestinal tract such as Sonne dysentery and giardia infestations cannot be ignored. The most reliable test of differential value is the oral glucose tolerance curve; this was normal in three of the four cases. It is necessary to ensure an adequate carbohydrate intake some time prior to the test, however, to obviate the false low values obtained with a previously prolonged low carbohydrate consumption. The low value obtained in the vitamin A absorption curves would suggest that larger therapeutic doses are required as a routine than by the normal child if adequate absorption of the vitamin is to be ensured.

Discussion

Multiple deficiency states such as anaemia, scurvy and rickets are commonly seen in long-standing cases of coeliac disease. It is apparent that these are nutritional defects, no doubt due to a restricted diet, since they can be controlled by the administration of appropriate vitamins and supplements to the diet. The essential defect in coeliac disease, namely, the mal-absorption of fats and carbohydrates, remains unexplained.

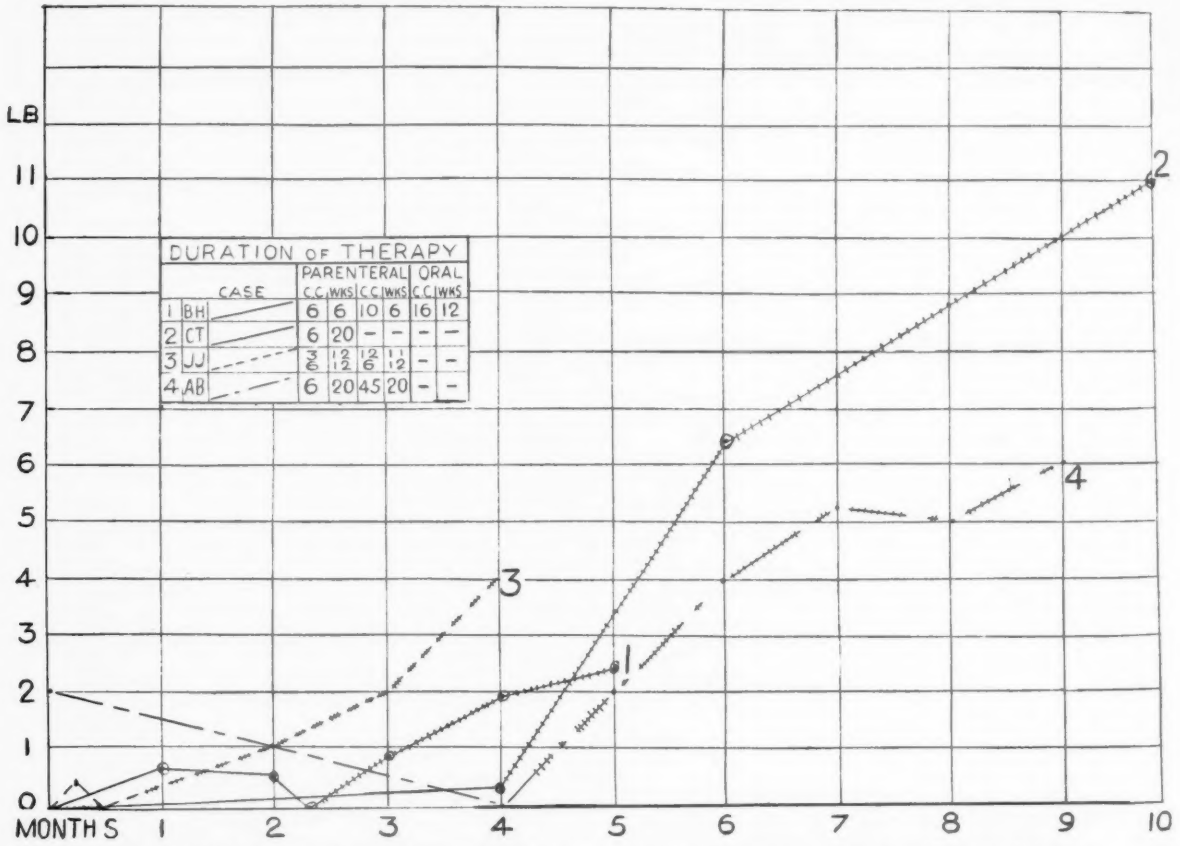


FIG. 3.—Weight gains in relation to duration of therapy in four cases of the ' coeliac syndrome.'

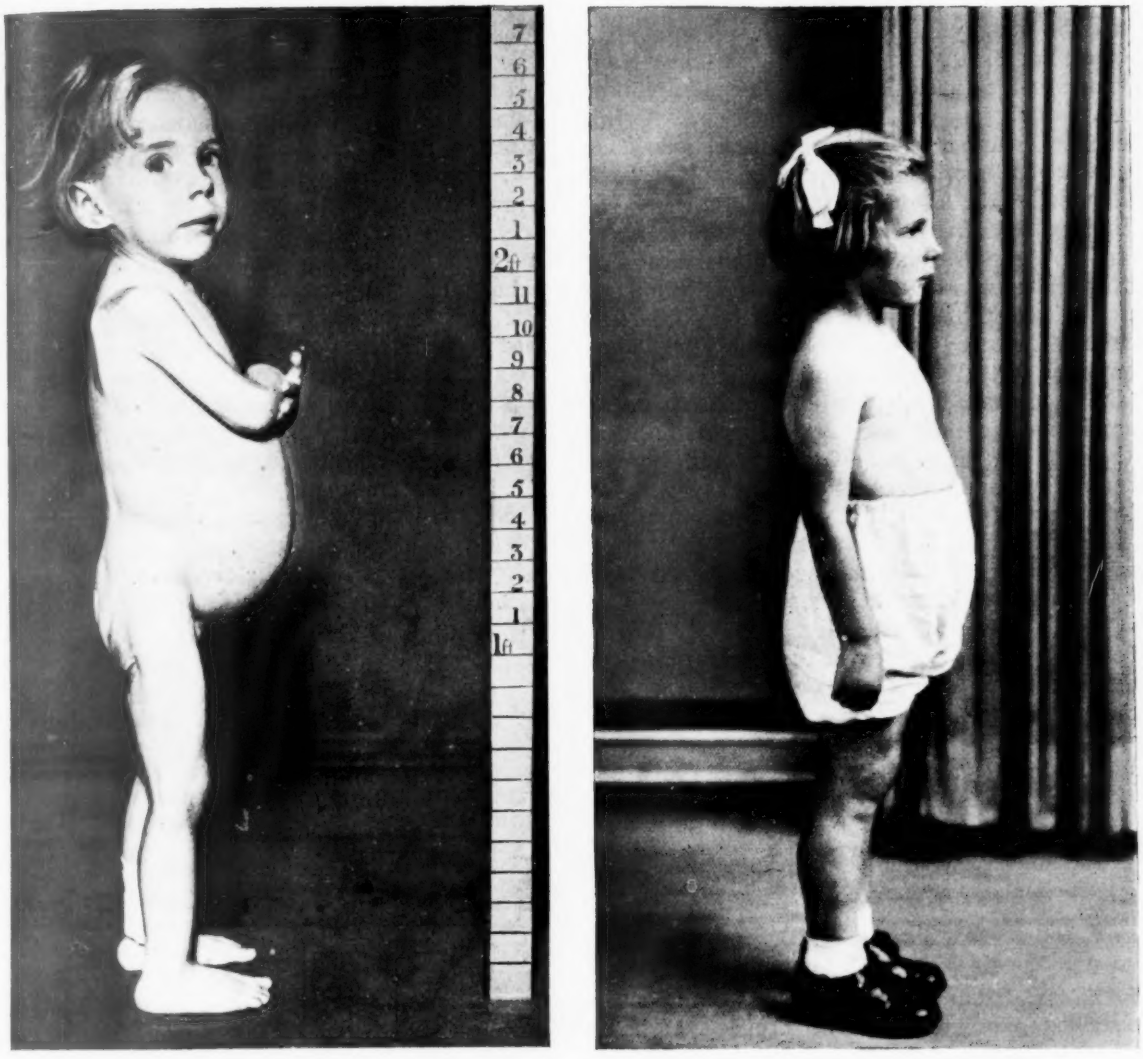


FIG. 4.—Case J. D. (No. 1, table 1). Before (age 2½) and after treatment (age 8 yr. 9 mth.).

The investigations of Ross (1937) contributed to the understanding of the disturbance of carbohydrate absorption in coeliac disease. By means of the oral and intravenous glucose tolerance curves he demonstrated that glucose was absorbed poorly from the small bowel and removed slowly from the blood in cases of coeliac disease. In other words, the characteristic oral curve is low or flat and the fall to normal after intravenous glucose slower than normal. Ross recognized that these findings were identical with those obtained in the normal child who has been kept on a low carbohydrate diet and whose carbohydrate intake is then increased.

Parsons (1938) reported the successful treatment of his cases with a low fat, high protein diet and gradually increasing amounts of carbohydrates, supplemented by weekly injections of a liver preparation (campolon). Although clinically they improved, he found that the oral glucose curves remained low, even after a prolonged period of therapy. However, May et al. (1941) reported that a significant improvement in the oral glucose curves occurred in their cases after three to six weeks of parenteral liver and vitamin B complex therapy.

A high carbohydrate diet appeared to be well tolerated from the clinical standpoint. No relapses of diarrhoeal or fermentative type of stools were noted while the children were under treatment, unless a definite upper respiratory tract infection occurred. In these instances tolerance to fat was also impaired and it was necessary to adjust the diet accordingly.

Since the oral glucose curve showed a return to the normal peak rise of 40 mgm. per cent. in only two of the nine cases who were tested both before and during treatment, and a rise of from 20 to 40 mgm. per cent. in five cases tested before and after treatment, it is debatable how far this treatment is responsible for an improvement in carbohydrate absorption. In addition, there is no clear evidence as to whether liver or vitamin concentrates might effect such an improved absorption. It is possible that the improvement in general health is followed by a return of normal bowel function, and that this change is independent of specific vitamin therapy. Further investigations regarding their effect on the utilization of glucose are necessary for the elucidation of this point.

May et al. (1941) reported a measurable improve-

ment in fat absorption within three to six weeks of parenteral therapy in fourteen of their cases.

Using vitamin A as a measure of fat absorption, he came to the conclusion that neither the reduced motility of the gut (a not uncommon characteristic of coeliac disease) nor bile salts nor the duodenal and pancreatic enzymes (which were normal on analysis) accounted for the fat malabsorption.

In three of the five patients here reported on whom vitamin A curves were obtained, both before and during treatment, improvement in fat absorption was observed. In the remaining two cases no improvement had occurred after 3 months (8, D. M.) and 11 months (10, Y. F.) of treatment.

The persistence of a high stool fat content in four cases in spite of intensive therapy and coincident with marked gains in weight and general improvement in health, requires comment (1, J. D.; 3, K. T.; 12, J. M.; and 16, B. F.). It implies that the defect in fat absorption was not corrected. It is possible that an irreversible change had occurred which could not be corrected by this therapy. It is also possible that return to normal function requires a longer time than was allowed between the tests for measure of fat absorption or that some patients require more prolonged treatment than others. It is well known that most children with coeliac disease improve gradually under various dietary managements, but in some few cases the symptoms persist into adult life. That some of the present cases are refractory, although still under treatment offers a challenge to the specific nature of the treatment as outlined above.

Summary

1. The treatment of twenty-six cases of idiopathic coeliac disease and four cases of ' coeliac syndrome ' with parenteral liver extract and vitamin B complex, given parenterally and orally is reported.

2. Satisfactory gains in weight and height, and improvement in general health were obtained in the early weeks of treatment and sustained over a period of months in the patients who received sufficiently intensive and prolonged therapy.

3. Less dramatic improvement and less satisfactory weight gains resulted when the parenteral liver extract was given in conjunction with an oral instead of parenteral vitamin B complex preparation.

4. The children were given and thrived on a normal balanced diet, during or after the initial weeks of treatment. The total stool fats improved in all but four cases and returned to normal in eighteen of twenty-six cases.

5. Slow improvement was commonly associated with the occurrence of upper respiratory infections.

6. In the secondary type of the disease, ' coeliac syndrome,' resulting from chronic foci of infection, improvement appeared to be hastened by intensive therapy with liver and vitamin B complex.

7. Vitamin A absorption curves were obtained from cases both before and during treatment, none of which returned to normal.

8. Oral glucose tolerance curves were obtained in cases both before and during treatment, some of which returned to normal.

Thanks are due to Messrs. Lederle & Co., Ltd., who kindly supplied the vitamin B complex, also to Dr. W. W. Payne who carried out the oral glucose tolerance tests, to Miss Charlotte Wood of the Oxford Nutrition Survey, who carried out the vitamin A absorption tests, and to Miss Nora Hair for her great help in preparing the graphs and tables.

References

Andersen, D. H., and Early, M. V. (1942). *Amer. J. Dis. Child.*, **63,** 891.
Breese, B. B., and McCoord, A. (1939). *J. Pediat.*, **15,** 183.
Gee, S. (1888). *St Bart's Hosp. med. Rep.*, **24,** 17.
Hardwick, C. (1939). *Arch. Dis. Childh.*, **14,** 279.
May, C., McCreary, J. F., and Blackfan, K. D. (1941). *J. Pediat.*, **21,** 289.
Parsons, L. (1938). *Brit. med. J.*, **2,** 929.
Ross, G. (1937). *Trans. R. Soc. trop. Med. Hyg.*, **30,** 33–50.
Snell, A. M. (1934). *Arch. intern. Med.*, **53,** 615.
Yudkin, S. (1941). *Biochem. J.*, **35,** 551.

ATROPHIC SCLEROSIS OF THE CEREBRAL CORTEX ASSOCIATED WITH BIRTH INJURY

BY

R. M. NORMAN, M.D.

(From the Burden Mental Research Department, Stoke Park Colony, Bristol)

Although the cerebral lesions of birth injury in the new born have been well studied, there is still considerable uncertainty as to the nature of their late neuropathological sequelae. This paper is concerned with one aspect only of this problem, namely, the relationship of birth injury to a particular histological type of cortical atrophic sclerosis (ulegyria) which may produce the clinical picture of cerebral diplegia or of cortical blindness. This form of gyral atrophy is uncommon, having been encountered only four times in 300 autopsies at Stoke Park.

Ford (1927) has given a good acount of the controversies as to whether atrophic sclerosis follows vascular accidents of birth or prenatal degeneration of neurones. McNutt's (1885) influential paper had stressed the importance of meningeal haemorrhage as a precursor of gyral atrophy, an explanation accepted by Gowers (1893) and Osler (1889). Collier's (1924) address to the Royal Society of Medicine did much to discredit the theory of meningeal haemorrhage, but his conclusion that atrophic sclerosis resulted from a primary degeneration of the nerve cells in foetal life did not take into account the other possible consequences of birth injury and failed to carry general conviction (Sachs, 1926; Wilson, 1940).

The investigations of Schwartz (1924, 1927; Schwartz and Fink, 1926) on the brains of infants dying at, or shortly after, birth put the pathology of birth trauma on a more solid foundation and his work has opened up new fields of research to the student of mental deficiency. Schwartz showed the hitherto unsuspected frequency of multiple intracerebral haemorrhages and softenings which occurred especially in the periventricular drainage area of the tributaries of the veins of Galen, and he also described diffuse lesions of the cortex which apparently represented early stages of atrophic sclerosis. In a series of older individuals he was able to trace the evolution of these recent lesions to their terminal states of porencephaly or sclerosis. He illustrated examples of gyral shrinkage and distortion, often associated with an apparent multiplicity of small convolutions and affecting in particular the parietal and occipital lobes.

This condition, named by Schwartz 'sclerotic microgyria,' appears to be identical macroscopically with that found in the cases described in this paper. The controversial problem is whether or not such changes are pathognomonic of birth injury, for there is no doubt that there are several etiologically distinct forms of ulegyria: prenatal, natal and postnatal varieties certainly exist. Since information concerning the early histories of cases coming to post-mortem examination in later life is often vague or equivocal, there is urgent need for pathological criteria by which the cortical sclerosis of birth injury may be recognized. This task of classification is complicated by the knowledge that functional circulatory disturbance probably plays a part in many forms of infantile encephalopathy, so that even if a lesion is shown to be of vascular origin it does not necessarily follow that trauma at birth is the responsible precipitating factor.

As a result of these considerations, it has been thought profitable to record three examples of gyral atrophy which have in common certain histological features indicative of a vascular pathogenesis, and to discuss the significance of birth injury in their etiology. It is by the collection of individual cases of this sort that a more precise classification of the causes of severe mental defect may eventually be made.

Report of cases

Case 1. P. S., a male, was admitted to Stoke Park Colony when 9 years old and died aged 16 years 5 months.

History prior to admission. The following information was given by the mother. The child was first born and illegitimate. He weighed 4½ lb. at birth, labour pains lasting only two hours. For nearly nine months he 'did nothing but scream and cry.' He suffered from frequent severe epileptic fits which twice necessitated the administration of chloroform. In the fourth year of life he 'seemed to improve a great deal,' but was still unable to attempt walking. There was no febrile illnesses during infancy. The father, 'a terrible drunkard,' deserted the mother and no further information concerning him is available.

Examination after admission. The patient was classed as an imbecile, having a mental age of 2 years 7 months as estimated by the Merrill-Palmer Scale in which he was undoubtedly handicapped by

physical disability, being able to use only his left hand in the performance tests. Speech was confined to the repetition of a few poorly articulated words. Neurological examination revealed an asymmetrical cortico-striate diplegia. The pupils reacted normally to light. Ocular co-ordination was poor and an alternating divergent squint was present. On smiling, the left side of the face moved considerably more than the right. Power of movement was greatly reduced in the right arm, the tendon reflexes of which were diminished by a plastic type of rigidity. Athetoid movements of the fingers were noted. In the left arm, movements and co-ordination were comparatively good. Spastic paresis of the legs was present with contractures of hamstrings and tendo Achillis of both sides. The patient could raise his legs but could not walk, stand, or sit up, without help. The knee jerks were equally brisk and obtainable from the whole extent of the subcutaneous surface of each tibia. The left ankle jerk set off ankle clonus. An extensor plantar response and Oppenheim's sign were noted on the left side. The

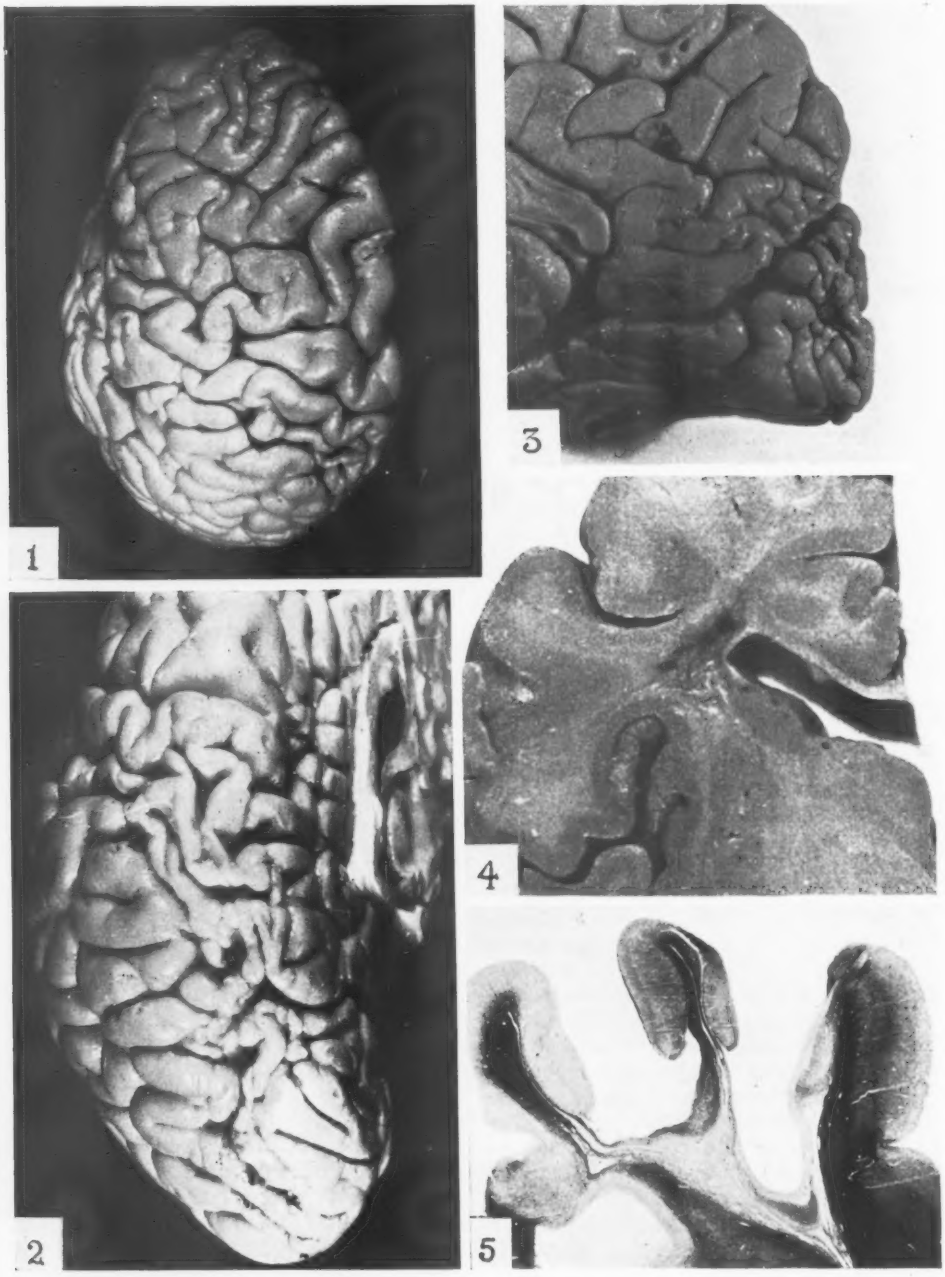


FIG. 1.—Case 1: Left hemisphere showing abnormal gyral pattern of the frontal lobe.
FIG. 2.—Case 1: Ulegyria of the left parieto-occipital area.
FIG. 3.—Case 1: Ulegyria of the right calcarine cortex.
FIG. 4.—Case 1: Coronal section of the left frontal lobe showing area of periventricular softening and dilatation of the lateral ventricle.
FIG. 5.—Case 1: Ulegyria of the left parietal cortex. Note the narrow streaks of demyelinization affecting the central cores of the two gyri on the left and the hemiatrophy of the gyrus on the right. Anderson's modified Kultschitsky-Pal stain ×5·5.

Wassermann reaction of the C.S.F. was negative and the fluid was also normal in other respects.

Prior to his death, which resulted from the perforation of an oesophageal ulcer, his mental and physical condition showed no obvious change, and there is no record of his having had an epileptic fit while in the Colony.

Pathological examination of the central nervous system.

MACROSCOPIC EXAMINATION. The brain was small, weighing with cerebellum and brain stem 1126 gm. Dura and leptomeninges were normal. There was conspicuous shrinkage and distortion of the gyri of the left superior parietal lobule at the margin of the great longitudinal fissure, involving the superior end of the post central gyrus and reaching posteriorly to within 2 cm. of the occipital pole (fig. 2). A similar condition was present on the medial aspect of the right hemisphere on both sides of the parieto-occipital fissure and along the beginning of the upper lip of the posterior calcarine fissure (fig. 3). On sectioning the brain in these areas it was seen that the deeper parts of the walls of these small gyri were more shrunken than their crowns. The point of transition between their bulbous crowns and elongated sclerotic stalks was often abrupt and sometimes a symmetrically placed indentation occurred on either side of the gyrus, producing, as it were, a neck beneath the expanded terminal portion. The pattern of the left frontal lobe was abnormal, there being little indication of a superior or inferior frontal sulcus (fig. 1). The right frontal lobe appeared more normal, though here also the superior frontal sulcus was short and ran obliquely into the great longitudinal fissure. On sectioning the brain in the coronal plane, symmetrically placed greyish areas of old softening were seen in the central white matter adjoining the anterior horns of the lateral ventricles, which were moderately dilated. This periventricular lesion was more marked on the left side (fig. 4). The body of the corpus callosum was thinner than usual for a brain of this size.

MICROSCOPIC EXAMINATION. Blocks of tissue were taken from representative areas of the cerebral cortex of both hemispheres, from different parts of the basal ganglia, brain stem and cerebellum. Sections were stained by standard methods for nerve cells, axis cylinders, neuroglia and lipoid.

CEREBRAL CORTEX. Examination of the left parieto-occipital and right occipital regions showed that the atrophied parts of the cortex had in common certain distinguishing features. The shrunken, constricted basal portions of such gyri showed intense neuroglial sclerosis with conspicuous sheaves of piloid glia separating an outer compact cortical layer from a deeper cystic part (fig. 8). In such areas nerve cells and myelinated fibres were usually absent, though in less severely affected gyri a few clusters of pyramidal cells remained, being sometimes arranged in two thin layers between which a streak of neuroglial scar passed upwards towards the crown of the convolution. Similar thin streaks of atrophy were seen in the white matter of the central cores (fig. 5). A small, sharply demarcated focus of total demyelinization * was usually present below the base of the shrunken gyrus. Here and there were scavenger cells containing lipoid. Holzer staining showed that dense neuroglial proliferation corresponded to this subcortical area of demyelinization, while a moderate gliosis affected the neighbouring white matter to a variable extent. The crowns of the atrophied gyri were often split by superficial indentations into a series of smaller convolutions, thus giving an abnormal appearance of complexity to the surface of the brain (fig. 6). Neuroglial sclerosis ceased abruptly at the margin of these nerve cell bearing parts of the cortex where, in myelin preparations, an abnormal density of darkly staining fibres was often seen (figs. 6 and 7).

The transition between these ulegyric parts and the macroscopically normal gyri was usually abrupt. Sometimes one half of a large convolution was totally atrophied, the remainder being normal, apart, perhaps, from a small hypermyelinated scar (fig. 5). It was found on microscopic examination that the sharp constrictions often seen in the walls of the less affected gyri corresponded to small, discrete neuroglial scars which were associated with hypermyelinized axis cylinders and formed short, laminar defects in the cortex, usually in its third layer. Another variation of this theme is seen in fig. 6 and 7. Here narrow neuroglial scars emerge from the area of subcortical sclerosis and curve upwards for a short distance into the wall of a neighbouring gyrus.

The parts of the cerebral cortex remote from these ulegyric areas showed little evidence of pathological change. In the left cornu Ammonis, however, severe neuroglial sclerosis was found throughout the major part of its extent and there was a typical pyramidal cell defect in the Sommer sector. The macroscopically normal paracentral convolution on the right side proved on section to contain a narrow band of laminar atrophy affecting the middle of the third layer accompanied by coarse, darkly staining myelinated fibres running parallel to its course. A mild, diffuse outfall of nerve cells affecting the third cortical layer and unaccompanied by glial proliferation was occasionally seen in sections taken from the frontal lobes of both sides. A few gitter cells containing lipoid were often seen around the small blood vessels of the central cores of white matter of gyri which were apparently normal in other respects.

CENTRAL WHITE MATTER. Gross demyelinization and neuroglial scarring were present in the areas of softening adjoining the lateral ventricles in the frontal lobes. In the loose mesh-works of this gliosis there were scattered scavenger cells containing lipoid. Thick sections showed a few poorly-staining and beaded myelinated fibres traversing the softened areas. The ' U ' fibres of the cortex adjacent to this area of softening were intact.

BASAL GANGLIA. The left thalamus showed marked nerve cell loss in the lateral nucleus associated with dense gliosis. Many of the remaining nerve cells were calcified. Myelinated fibres were not obviously reduced in this area, but no état marbré was seen. The external geniculate body was intact, as were putamen, globus pallidus and caudate nucleus of the left side.

The right thalamus showed a small area of complete demyelinization and neuroglial sclerosis in the dorsal part of the lateral nucleus (fig. 10). A few calcified nerve cells were present near this focus. The external geniculate showed degeneration (retrograde) and gliosis in its deeper laminae. In the

* In order to avoid a cumbersome terminology, this term has been used to denote an absence of myelin. If the lesion occurred at, or before birth, the majority of axis cylinders would, of course, be unmyelinated.

FIG. 6.—Case 1: Sclerotic microgyria of the right occipital lobe. Kultschitsky-Pal ×3.
FIG. 7.—Case 1: Adjoining section to that shown in fig. 6. Holzer stain ×3.
FIG. 8.—Case 1: Gliosis in the wall of an atrophied gyrus. Mallory's phosphotungstic acid hæmatoxylin ×80.
FIG. 9.—Case 1: Right caudate nucleus. Coronal section showing état marbré. Kultschitsky-Pal ×5.

right caudate nucleus a small focus of necrosis, similar to that seen in the thalamus, was found at the junction of head and body. Radiating from this area there was a well-marked état marbré (fig. 9). The putamen and globus pallidus were intact.

BRAIN STEM. The left pyramidal tract was smaller and slightly less well myelinated than the right. This abnormality was seen in sections from the pons, medulla, and cervical cord, but no demonstrable gliosis was present.

Case 2. G. H., a male, was admitted to the Colony when 7 years 10 months of age and died one month later.

History prior to admission. The patient was the firstborn child of highly intelligent parents whose family history was free from neuropathic taint. Another sib, four years younger, is normal. Both parents were interviewed and gave me the following information:—

The mother's age at the birth of her son was 36 years. During pregnancy her health was good apart from troublesome vomiting for the first four months. The baby was full term. Labour pains began at 3 a.m. and at 11.30 a.m. the family doctor delivered the child by forceps.

The child was apathetic for the first two days. His condition then deteriorated, he became weak

and unable to take his feeds and was admitted to the Birmingham Children's Hospital under Prof. L. G. Parsons, to whom I am indebted for the following notes:—' On admission he was a normally developed baby but slightly jaundiced; there was no bulging of the fontanelle. On the day after admission he had some slight twitching of the right eye and right leg, but this did not recur. The child was in hospital for six days, during which time he put on 3 oz. in weight.' During his stay in hospital he was fed by his mother's milk and when he came home took the breast fairly well. There was no obvious paralysis, but he had a fit when six weeks old. Frequent fits were noted from the age of 4 months and at 7 months they were of daily occurrence. He paid no attention to moving objects, nor could he sit up or even raise his head for very long.

Examination after admission. A thin, apathetic child with slight pigeon breast. Height 3 ft. 6 in.; weight 2 st. 1 lb. A neurological examination showed a generalized excessive muscle tone, all tendon reflexes being markedly exaggerated. The abdominal reflexes were absent and both plantar responses were extensor. There was some contracture of the hamstrings. He was incapable of purposive movement and exhibited coarse, irregular jerky movements of choreic type, present at rest and considerably exacerbated on cutaneous stimulation. He could not hold up his head or sit up and was doubly incontinent. The skull was asymmetrical in that the right occipito-parietal region was relatively flattened.

The blood Wassermann reaction was negative.

On admission he had to be bottle fed but later became capable of swallowing fluids by spoon. Several major and a few minor fits occurred daily until controlled by luminal. Death resulted from bronchopneumonia.

Pathology of the central nervous system.

MACROSCOPIC EXAMINATION OF THE BRAIN. Weight 1105 gm. (left hemisphere 460 gm.; right hemisphere 510 gm.; cerebellum and brainstem 135 gm.). The leptomeninges showed slight thickening and oedema. The left postcentral gyrus was narrow and shrunken, its crown showing two shallow, irregular grooves running parallel with the long axis of the convolution. The gyri of the left frontal lobe were somewhat narrower and more tortuous than those of the rignt side. On coronal section, shrinkage of the deeper parts of the gyri of the left frontal lobe was apparent, the posterior portions of the second and third frontal convolutions being affected in this manner, the gyral crowns, however, being somewhat swollen and friable. There was slight dilatation of the left frontal horn of the lateral ventricle.

MICROSCOPIC EXAMINATION. CEREBRAL CORTEX. The leptomeninges showed mild fibrous thickening but were not adherent to the cortex. The anterior wall and crown of the left postcentral gyrus showed dense myelinated fibres arranged in a narrow band occupying the middle of the grey matter (fig. 11). Holzer staining demonstrated thin glial scars corresponding to the position of this abnormal myelinization. In this part of the grey matter nerve cells were absent and a diffuse loss of neurones was also seen in the adjoining cortex. In the proximity of arterioles in the sclerosed areas a few scavenger cells filled with lipoid were commonly present. The frontal gyri of the left side also showed several myelinated scars of the same type, more particularly in their walls (fig. 12 and 13). It was observed that in the parts of the grey matter subjacent to these linear defects the normal radial fibres were absent, their place being taken by numerous irregularly arranged myelinated axis cylinders. The cortex above the scar, however, was almost devoid of myelin except for a narrow layer of tangential fibres near the surface of the gyrus.

In general, the nerve cells of the cortex stained very poorly with cresyl violet or toluidine blue, the cell bodies being scarcely visible. The Betz cells stained diffusely and did not appear to be numerically deficient. Both hippocampi and visual areas were intact. Arterioles and often capillaries were congested and signs of terminal oedema of the brain were evident in the form of dilated perivascular and pericellular spaces. A diffuse loss of cells in the third layer, unaccompanied by gliosis, was commonly seen in the frontal and parietal lobes.

OTHER PARTS OF THE BRAIN. Sections of the left thalamus made in the coronal plane at the level of the external geniculate body showed conspicuous atrophy of nerve cells with accompanying gliosis in the region of the nucleus ventralis posterolateralis. In the medulla both pyramidal tracts were well myelinated, the left, however, being the smaller. Sections from cervical, thoracic and lumbar levels of the spinal cord revealed no abnormality with regard to myelin, glia or nerve cells.

Case 3. H. M., a male, was admitted to the Colony when 15 years old and died aged 17 years 5 months.

History prior to admission. The patient was the sixth child of a family of seven. The mother's age was 38 years at the time of his birth. The other six sibs were mentally and physically normal according to the mother (1943) who has supplied the following information. The infant was full term. The mother could recollect no details about the birth, which she regarded as normal. The infant took the breast well and no anxiety was experienced until the fourth day, when a convulsion occurred and it was noticed that the baby was jaundiced. The mother cannot remember how long the jaundice persisted, but the child's health was apparently unaffected. Fits recurred frequently during infancy—' Every day, but sometimes he would have them more than I can remember.'

He began to walk at the age of three years.

Examination after admission. The patient was classed as an imbecile verging on idiocy, but on account of grossly impaired vision an accurate estimate of his mental abilities was impossible. Speech was limited and articulation defective. He could not feed or dress himself. Spontaneous activity was largely limited to rocking himself forwards and backwards on his chair. Physically he was undersized and small headed. A neurological examination at this time gave the following information. Pupils reacted to light but no response was elicited to accommodation as he was unable to fixate an object. There was an alternating divergent strabismus, and an error of refraction of about +5 in both eyes. The fundi were difficult to examine owing to constant rolling of the eyes under the lids but the discs were seen to be pale, though not definitely atrophic (Mr. A. E. Iles). In the upper

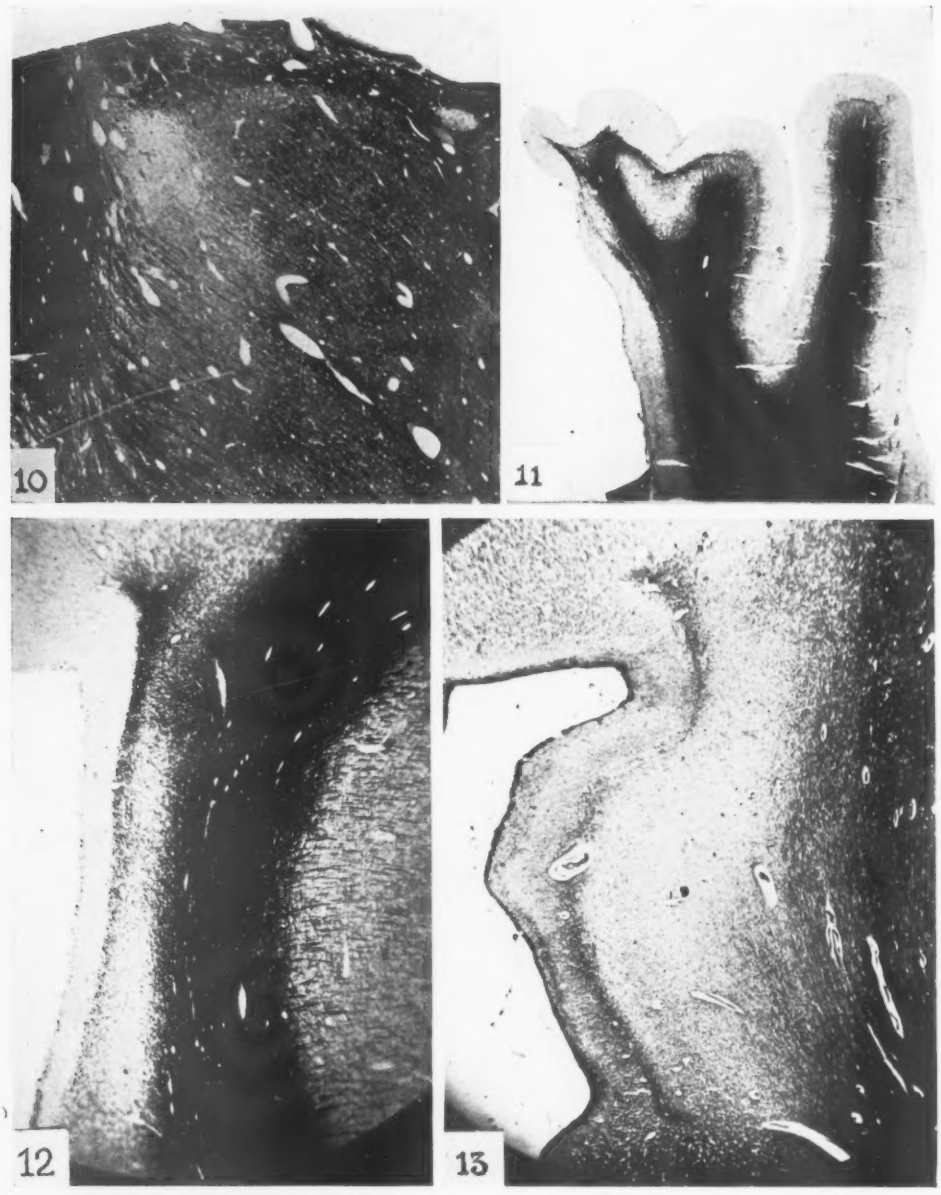


FIG. 10.—Case 1: Right thalamus showing small focus of necrosis. Kultschitsky-Pal ×6.
FIG. 11.—Case 2: Left post-central gyrus (on left) showing laminar hypermyelinization. Kultschitsky-Pal ×3.
FIG. 12.—Case 2: Left frontal cortex showing laminar hypermyelinization in middle zone of grey matter in gyral wall. Kultschitsky-Pal ×13.
FIG. 13.—Case 2: As in fig. 12 (adjacent part of block) showing glial scar. Mallory's phosphotungstic acid haematoxylin ×13.

limbs the muscle and tendon reflexes were brisk and equal. In the legs the knee jerks were equal and exaggerated, being obtained from the whole length of the leg. Ankle jerks were also equal and very brisk. The abdominal and cremasteric reflexes were present on both sides. An extensor plantar reflex was obtained on the left side.

During his life in the Colony his neurological condition remained stationary and he suffered from major epileptic fits at irregular intervals. Death resulted from phthisis.

Pathology of Central Nervous System.

MACROSCOPIC EXAMINATION OF THE BRAIN. The brain was small for a boy of 17 years, weighing only 1061 gm. with cerebellum and brainstem. The region of the left posterior calcarine fissure was occupied by a group of minute convolutions (fig. 14). A similar appearance was presented by the lower lip of the calcarine fissure of the opposite side, and a few small formations of the same sort were just visible on the surface of the right hemisphere emerging from the upper part of the post-central sulcus. Sclerotic atrophy was evident in the depths of some of the sulci in the left precuneal region. The general convolutional pattern of the brain was not otherwise abnormal, except perhaps in the right temporal lobe where the superior temporal sulcus was unusually short.*

* A photograph of this hemisphere appears in 'A cerebral Atlas.' Berry, R. J. A., Oxford University Press, 1938. Fig. 223.

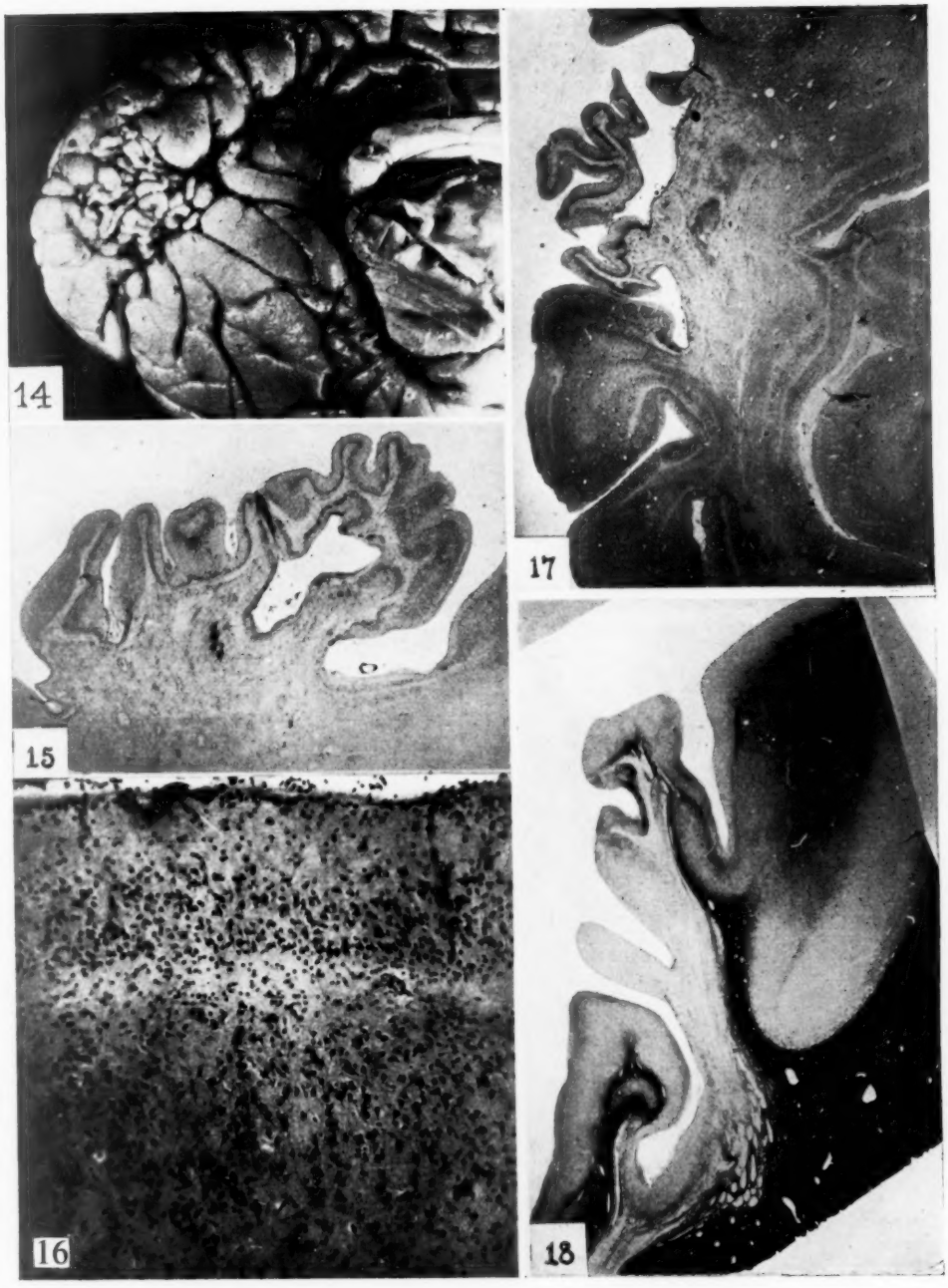


FIG. 14.—Case 3: Left calcarine area showing microgyria.
FIG. 15.—Case 3: Microgyria from left occipital lobe. Cresyl violet ×4·4.
FIG. 16.—Case 3: Laminar defect in cortex of left precuneal region. Cresyl violet ×60. Note the irregular disposition of the nerve cells in the deeper layers.
FIG. 17.—Case 3: Right occipital lobe. Coronal section showing microgyria filling in the defect formed by the atrophy of the calcarine cortex. Cresyl violet ×3·7.
FIG. 18.—Case 3: Microgyria arising from the posterior wall of the right post-central gyrus. Kultschitsky-Pal ×4.

MICROSCOPIC EXAMINATION. Sections prepared from the microgyric areas of both occipital poles and the upper right postcentral area revealed a type of structure already encountered in case 1, with this qualification, that whereas in the first case the crowns of the sclerosed gyri usually showed only shallow superficial indentations, in the present instance the process of splitting into small subconvolutions had often proceeded further and had resulted in the creation of numerous, discrete microgyric formations. In nerve cell preparations these were seen to consist of thin loops of pyramidal cells, sometimes having a wavy or festoon-like outline (fig. 15). The common stem from which these small gyri sprang was invariably heavily sclerosed, the edge of the neuroglial proliferation ceasing abruptly at the neurone-bearing crowns, where dense whorls of hypermyelinated fibres were often present. The striate areas of both sides were extensively atrophied, each posterior calcarine fissure being

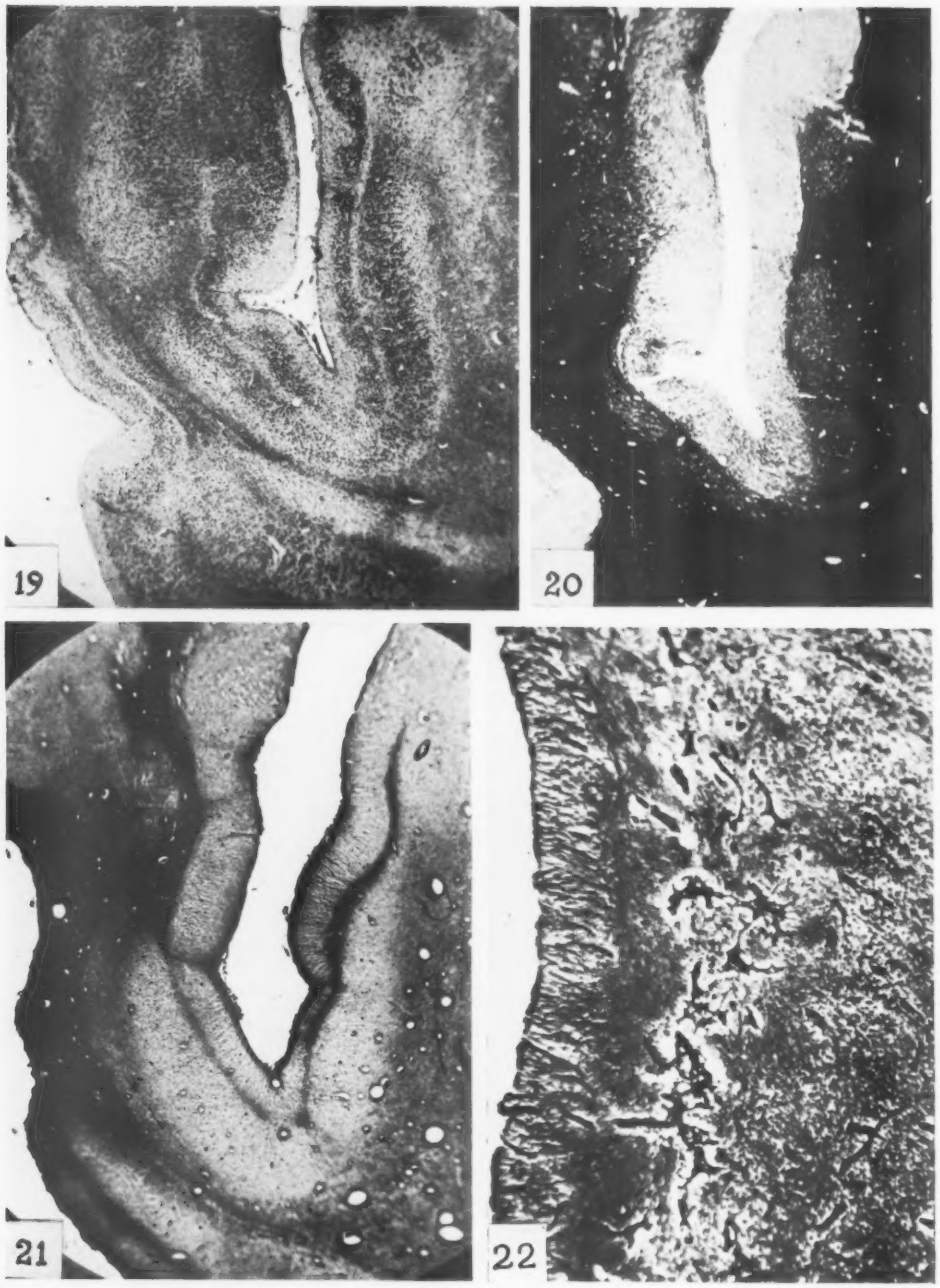


FIG. 19.—Case 3: Laminar defect in the depths of a gyrus in the left precuneal region. Cresyl violet ×12·8.
FIG. 20.—Case 3: Adjoining section to that of fig. 19. Kultschitsky-Pal ×12·8.
FIG. 21.—Case 3: As in fig. 20. Holzer stain ×12·8.
FIG. 22.—Case 3: Sclerotic blood vessels in a laminar defect of the cortex. Hortega's silver carbonate method for astrocytes ×60.

represented by a depression filled with the microgyric convolutions already described, which appeared to have grown down from the region of the parieto-occipital fissure and to have filled up the space left by the destruction of the calcarine visual area (fig. 17). The anterior calcarine fissures were macroscopically normal but the gyri on either side occasionally showed short linear hypermyelinated scars in their walls. Laminar atrophy of the cortex was a conspicuous feature of the neighbouring occipital gyri (fig. 17) and was also present in the depths of the gyri of the left precuneal area where 'U'-shaped cortical defects could be seen by the naked eye in the depths of the sulci. The nerve cell, myelin and glial, abnormalities of such regions are shown in fig. 16, 19, 20 and 21. It will be seen that the cortex is divided into two layers by a dense neuroglial scar, the inferior limit of which is occupied (in myelin preparations) by a line of darkly myelinated fibres. In the deeper layers of the cortex the normal radial bundles are replaced by a close network of fibres which occasionally show typical plaques fibromyéliniques. The transition between this laminar defect and the normal cortex is abrupt and occurs at the fourth, or granular layer. The blood vessels in the linear streaks of atrophy showed

adventitial thickening (fig. 22). As in the other cases, a few compound granular corpuscles were sometimes seen near the walls of blood vessels.

The microgyria of the right parietal area originated from the posterior wall of the postcentral sulcus and showed the familiar combination of sclerosis, linear atrophy and hypermyelinization (fig. 18). Nerve cells were diminished in the third layer of the neighbouring pre- and post-central gyri. Elsewhere in the cortex, basal ganglia, cerebellum and brain stem no evidence of a destructive process was discovered. Both external geniculate bodies, however, showed extensive retrograde degeneration.

Comment

In attempting to assess the probability of birth injury having caused the atrophic sclerosis of the present cases, reliance has necessarily to be placed upon indirect evidence. The lesions were of long standing, and although small groups of microglial phagocytes clearly indicated a destructive process, all evidence of haemorrhage, if such had indeed occurred, had long since vanished. The clinical histories did not support the theory of a post-natal pathogenesis, no febrile illness in infancy likely to produce cerebral atrophy having been observed. The family histories gave no hint of a genetic cause for the condition, nor, as will be seen later, were the pathological findings appropriate to an heredo-degenerative process. Evidence of a more positive kind in favour of birth injury may be looked for in the birth histories, in the histological character of the ulegyria and in the distribution of the cerebral lesions, for it is well known that birth trauma has a predilection for certain parts of the brain. These points will now be considered in reference to the present cases.

The clinical histories are suggestive of trauma in the first two cases. The rapid birth of a first born infant weighing only 4½ lb., as in case 1, is an event fraught with dangerous possibilities. Some degree of prematurity is likely; a condition which predisposes to trauma because of the thinness of skull and weakness of cerebral veins (Ylppö, 1924). Probably the relative insensibility of the respiratory centres to carbon dioxide known to exist in premature infants (Levine and Gordon, 1942) is an added factor of importance. In the second case, that of a first-born male infant, in this instance full term and delivered by forceps, the general condition deteriorated two days after birth, with apathy and refusal to take feeds, as has repeatedly been recorded in birth-injured children (Rydberg, 1932). The slight focal epilepsy displayed in the early days is also indicative of localized brain injury. In the third case there is no history of abnormal labour and the onset of convulsions on the fourth day, though consistent with birth injury, might perhaps with equal justification be ascribed to a prenatal cause.

The histological character of the ulegyria is more in keeping with a vascular than a degenerative pathogenesis. The lesions affected small areas of the cortex, were relatively sharply circumscribed, and were grouped around foci of special intensity which involved the deeper parts of the gyri and adjoining subcortical white matter. This special vulnerability of the gyral wall to anoxaemia has been noted by Doring (1936) in deaths from drowning. No less characteristic of a vascular process was the presence in all three cases of narrow streaks of atrophy usually affecting the middle zone of the cortex and ending abruptly in the granular or fourth layer of neighbouring gyri. Arteriolar lesions of similar distribution are common in cerebral vascular disease of adult life (Neubürger, 1930). Alajouanine and Hornet (1936) have recorded an instructive example of extensive laminar atrophy with a small focus of cortico-subcortical softening in an elderly arteriosclerotic patient. There is a close resemblance between such a picture and the occipital lesions present in case 3. The narrow, elongated hypermyelinized scars, so frequently seen in the present cases, are also a feature of the uncommon form of gyral sclerosis known as 'the granular atrophy of Spatz' (Pentschew, 1933). This condition is characterized by a shrinkage and puckering of the crowns of convolutions and appears to be the consequence of cerebral anoxaemia induced by a variety of predisposing vascular diseases and also by carbon monoxide poisoning.

While there is thus good reason for believing that the atrophic sclerosis in the present cases is the result of a vascular rather than a primarily degenerative process, the problem still remains as to whether these lesions occurred at birth or during the later stages of foetal development. This decision is made the easier in the first case by the fortunate coincidence of subcortical lesions highly characteristic of birth injury, namely, the bilateral periventricular areas of softening in the central white matter of the frontal lobes. In view of Schwartz's observations, there can be little doubt that this condition is the late sequela of haemorrhage or softening in the drainage area of the terminal veins, a conclusion to which further support is given by the glial scarring and foci of necrosis in the right thalamus * and caudate nucleus, the latter associated with état marbré. Marbling of corpus striatum and thalamus has been recorded in several cases having a history suggestive of birth injury (Scholz et alia, 1938; Meyer and Cook, 1936), but it is rare to find such marked periventricular softening of the white matter in the same brain. Among the many examples of the latter lesion which have been recorded by Schwartz were some which showed, in addition, diffuse sclerosis and shrinkage of cortical gyri. It is thus highly probable that the ulegyria of the parieto-occipital region found in case 1 of the present series dated from a lesion sustained during birth and not from a hypothetical prenatal abnormality. It might be urged that the unusual convolutional pattern of the left frontal lobe (fig. 1) is indicative of prenatal malformation and that

* The atrophy affecting the lateral nuclei of the left thalami of cases 1 and 2, and the external geniculate bodies in cases 1 and 3, are clearly examples of retrograde degeneration following partial destruction of the parietal and calcarine cortices respectively.

lesions found elsewhere in the cortex are, therefore, likely to be of prenatal origin also. Were this case the first of its kind to be reported this argument might have weight, but, as has been pointed out above, the combination of sclerotic cortical lesions and central softening in the distribution of the terminal veins, the latter so typical of birth injury, has been described in other cases by Schwartz. Moreover, variations from the text-book gyral pattern, though common in the brains of mental defectives, also occur in the presumed normal, and their pathological significance, except in gross instances, is uncertain. Even if this gyral configuration be considered an undoubted malformation, this finding is relevant to the pathogenesis of the ulegyria only in as much as malformation may predispose to birth injury. Whilst the possibility of a double pathology for the mental deficiency of the first patient cannot be denied, birth injury still remains the most probable explanation of the cortical atrophy.

In case 2, no such informative periventricular lesions were present, the essentially laminar atrophy being confined to the grey matter of the cortex. Its distribution was consistent with the clinical history which had suggested a mild birth injury affecting the frontal portion of the left hemisphere. The extent of atrophy seems insufficient to account for the idiocy and symmetrical paresis manifested during life. This discrepancy may be made good by taking into account the conspicuous nerve cell loss noted in areas remote from the grosser lesions; but the relationship of this commonplace pathological finding to birth injury is conjectural. It is possible that the diffuse loss of nerve cells in the third layer of the cortex may have been the result of repeated epileptic 'insults,' themselves conditioned by the original foci of sclerotic atrophy. An example of such an association of epilepsy with progressive cortical damage in early infancy has been recorded by Levin (1936).

In case 3 the bizarre form of the microgyria certainly suggests a prenatal origin, and, in a closely similar case (Norman, 1937), that interpretation was formerly favoured. In view of the findings in case 1, it would seem inadvisable to dismiss birth injury from consideration. The clusters of small gyri arising from a common sclerotic stem, which were the characteristic feature of case 3, may be regarded simply as a further stage in the evolution of such partially split gyral crowns as were observed in case 1. While it is true that the undulating or festoon-like arrangement of the nerve cells in some of the small gyri is reminiscent of what is sometimes found in microgyria of undoubted prenatal origin (Bielschowsky, 1915), the two conditions are dissimilar in other respects. It is unlikely that this sclerotic microgyria was the result of a destructive process superimposed on a pre-existing malformation. On the contrary, the way in which clusters of small convolutions had filled in the depression formed by the atrophied calcarine cortex strongly suggested that the development of the microgyria post-dated an initial lesion of the hemisphere. There is thus good reason for regarding the microgyria of this case also as a postnatal malformation conditioned by a vascular lesion. Although direct proof of birth injury is lacking, it is difficult to suggest a more probable alternative cause.

No attempt will be made here to review the theoretical explanations as to the cause of intracranial haemorrhage or brain softening in the newborn.

Rydberg (1932) has given a good survey of this aspect of the subject. Two points relevant to this discussion may be mentioned. The first is that Holland's (1923) demonstration of the manner in which the great veins of Galen may become obstructed at their junction with the straight sinus owing to excessive moulding of the head seems to provide an adequate explanation for the periventricular haemorrhages so characteristic of birth injury. Secondly, the great diversity of cerebral lesions which may apparently be associated with birth trauma, ranging from massive porencephaly to a microscopic plaque fibromyélinique, is inexplicable on the basis of simple damage to individual blood vessels. Ricker's (1924) conception of functional circulatory disturbance provides a valuable unifying principle, the application of which to the pathology of birth injury clarifies many formerly obscure problems.

Summary

Clinical and pathological details have been given of three cases of severe mental defect dating from early infancy. The mental defect was associated with cerebral diplegia in the first two cases and cortical blindness in the third. The brains showed a form of atrophic sclerosis or ulegyria affecting relatively small areas of the cerebral cortex in an asymmetrical manner. The atrophy was most marked in the basal parts of the gyri and usually involved a small part of the subjacent white matter. The less affected gyral crowns often showed partial or complete subdivision into smaller microgyric convolutions, which tended to be hypermyelinated. Clear-cut laminar defects in the middle of the grey matter were typical features of the atrophic gyri and were also found radiating from the atrophied parts of the cortex into otherwise intact neighbouring convolutions. These lesions were associated with thin streaks of neuroglial sclerosis and accompanied by darkly staining myelinated fibres running parallel with their course. The first case, in addition to ulegyria, showed lesions in the periventricular drainage area of the terminal veins in the form of bilateral areas of softening in the central white matter of the frontal lobes and small foci of necrosis in the right thalamus and caudate nucleus, the latter accompanied by état marbré. The similarity of these findings with those previously reported by Schwartz in cases of birth injury, together with histories suggestive of trauma in the first two cases, make it highly probable that this form of gyral atrophy is a late sequela of birth injury.

Thanks are due to Dr. R. M. Bates, Medical Superintendent of Stoke Park, for permission to publish information derived from the Colony records.

References

Alajouanine, T., and Hornet, T. (1936). *Rev. neurol.*, 65, 1532.

Bielschowsky, M. (1915). *J. Psychol. Neurol., Lpz.*, **22**, 1.

Collier, J. S. (1924). *Brain*, **47**, 1.

Doring, G. (1936). *Virchows Arch.*, **296**, 666.

Ford, F. R. (1927). Cerebral birth injuries, Lond., Medicine monographs, **2.**

Gowers, W. R. (1893). A manual of diseases of the nervous system, Lond., 2nd ed.

Holland, E. (1923). *J. Obstet. Gynaec.*, **29**, 549.

Levin, P. M. (1936). *Arch. Neurol. Psychiat.*, **36**, 264.

Levine, S. Z., and Gordon, H. H. (1942). *Amer. J. Dis. Child.*, **64**, 274.

McNutt, S. J. (1885). *Amer. J. med. Sci.*, **89**, 58.

Meyer, A., and Cook, L. C. (1936). *J. Neurol. Psychopath.*, **16**, 341.

Neubürger, K. (1930). Bumke's Handbuch der Geisteskrankheiten, Bd. II. Berlin.

Norman, R. M. (1937). *J. Neurol. Psychiat.*, **1**, 1.

Osler, W. (1889). Cerebral palsies of children, Lond.

Pentschew, A. (1933). *Arch. Psychiat. Nervenkr.*, **101**, 80.

Ricker, G. (1924). Pathologie als Naturwissenschaft, Berlin.

Rydberg, E. (1932). *Acta path. microbiol. scand., Supp.*, **10.**

Sachs, B. (1926). *Amer. J. med. Sci.*, **171**, 376.

Scholz, W., Wake, J., and Peters, G. (1938). *Z. ges. Neurol. Psychiat.*, **163**, 193.

Schwartz, P. (1924). *Ibid.*, **90**, 263.

—— (1927). *Ergebn. inn. Med. Kinderheilk.*, **31**, 164.

——, and Fink, L. (1926). *Z. Kinderheilk.*, **40**, 427.

Wilson, S. A. K. (1940). *Neurology*, Lond., **2**, 760.

Ylppö, A. (1924). *Z. Kinderheilk.*, **38**, 32.

PROGNOSIS AND TREATMENT OF PNEUMONIA IN CHILDREN

BY

F. L. KING LEWIS, M.R.C.S., D.C.H.

Late Registrar to the Children's Department, Westminster Hospital and Registrar, Hospital for Sick Children, Great Ormond Street

Although the number of cases of pneumonia treated in the Hospital for Sick Children, Great Ormond Street, during the past five years has been relatively small, it may be helpful at this time to attempt to evaluate the merits of the different sulphonamides used, and to compare them with the results of treatment in the pre-sulphonamide years. The series in this report includes two groups, the pre-sulphonamide group of 100 children, admitted during the three years, 1936–38, and the sulphonamide group of 127 children, admitted during the five years, 1939–43. The number of medical beds was greatly reduced at the beginning of the war, and despite a gradual increase is still much below the pre-war figure.

Patients dying within twenty-four hours of admission, or in whom signs of improvement had set in before treatment was begun are not included (Elliott, 1941). Apart from these two points, the series is unselected. The organisms have not been cultured, but each case has been classified as broncho- or lobar pneumonia according to clinical signs and x-ray appearances.

Three sulphonamides were used in this series:

Sulphapyridine—almost exclusively from 1939–41;
Sulphapyridine and sulphadiazine in 1942; and
Sulphamezathine—in about two-thirds of the cases in 1943.

The number of children treated with other sulphonamide drugs was too small to warrant inclusion in this report.

Comparison of mortality in the pre-sulphonamide and sulphonamide groups and the effect of age

Reference to table 1 shows that the mortality rate in the age group 0–6 months was reduced from 80 per cent. to 11·1 per cent. which seems significant even with such small numbers. In the older age group 2–12 years, pneumonia is not a killing disease and the fall from 5·2 per cent. to 2·2 per cent. is less striking.

The average age of the children in the two groups was:

Pre-sulphonamide	..	3 years and 1 month
Sulphonamide	..	1 year and 8 months

The lowering of the age group admitted to hospital may be due partly to evacuation of the older children from London, and to the fact that the introduction of sulphonamides has enabled the general practitioner to treat the milder cases in older children in their own homes with more confidence.

Evaluation of the therapeutic effect of three sulphonamide drugs

Evaluation of the merits of the sulphonamide drugs is best made by a comparison of mortality rates, response to treatment and incidence of complications and toxic effects (Flippin et al., 1943).

(a) Percentage mortality. Sulphamezathine has a mortality rate in this series of 3·7 per cent. compared with 9·9 per cent. for sulphapyridine and 11·5 per cent. for sulphadiazine (see table 2).

(b) Response to treatment. The response to treatment was estimated by an analysis of the number of days before the patient was apyrexial and improving, as suggested by Peters and Easby (1943). With sulphamezathine 63 per cent. responded within two days and only 7·4 per cent. failed to respond within five days. The corresponding figures for sulphapyridine were 45 per cent. and 15·5 per cent. and for sulphadiazine 46·2 per cent. and 7·7 per cent. (see table 3). It is of interest to note that the average duration of the febrile period of pneumonia was reduced from 10·3 days in the pre-sulphonamide group to 3·2 days in the sulphonamide group.

(c) Complications. The incidence of complications—empyema, meningitis, otitis media—was low and shows no significant variation with the three drugs used.

(d) Toxic effects. Sulphapyridine appeared to be the most toxic of the drugs used, resulting in vomiting and rashes in some of the older children. One case of haematuria and one of anuria lasting five days (King Lewis, 1944) were also noted. A number of cases of haematuria have been noted following the use of sulphadiazine in other conditions and renal complications have been reported in the literature, but no toxic effects were found with either sulphadiazine or sulphamezathine in this series. With the latter, however, crystals were found in the urine on one occasion, but no red blood cells were seen.

TABLE 1

MORTALITY IN PRE-SULPHONAMIDE AND SULPHONAMIDE GROUPS AND EFFECT OF AGE

	Pre-sulphonamide (1936–38)			Sulphonamide (1939–43)		
	No. of cases	No. of deaths	Percentage mortality	No. of cases	No. of deaths	Percentage mortality
			Age 0–6 months			
Broncho	9	7		19	2	
Lobar	1	1		8	1	
TOTAL	10	8	80	27	3	11·1
			Age 6 months to 2 years			
Broncho	19	6		26	6	
Lobar	13	1		28	1	
TOTAL	32	7	21·9	54	7	13
			Age 2–12 years			
Broncho	26	3		22	1	
Lobar	32	0		24	0	
TOTAL	58	3	5·2	46	1	2·2
TOTAL all ages	100	18	18	127	11	9

TABLE 2

COMPARISON OF MORTALITY RATES WITH SULPHONAMIDES

Age	Sulphapyridine			Sulphadiazine			Sulphamezathine		
	Cases	Deaths	Per-centage mor-tality	Cases	Deaths	Per-centage mor-tality	Cases	Deaths	Per-centage mor-tality
0–6 months	11	2		7	1		3	0	
6 months to 2 years	38	4		11	2		10	1	
2–12 years	22	1		8	0		14	0	
TOTAL all ages	71	7	9·9	26	3	11·5	27	1	3·7

(NOTE.—Three cases from table 1 were treated with more than one sulphonamide and are therefore omitted from tables 2 and 3.)

TABLE 3

ESTIMATION OF RESPONSE TO TREATMENT

No. of days before patient was apyrexial and improving		2	3	4	5	6 or more	TOTALS	
							Cases	Deaths
Sulphapyridine	Cases	32	12	6	3	11	71	7
	Per cent. of total	45	16·9	8·5	4·2	15·5	—	9·9
Sulphadiazine	Cases	12	6	3	0	2	26	3
	Per cent. of total	46·2	23·1	11·5	0	7·7	—	11·5
Sulphamezathine	Cases	17	4	2	1	2	27	1
	Per cent. of total	63	14·8	7·4	3·7	7·4	—	3·7

The results of treatment with sulphamezathine therefore compare favourably with sulphapyridine and sulphadiazine, showing the lowest mortality rate, the most rapid response to treatment and freedom from toxic effects. It should be emphasized, however, that this drug has been used only in one year (1943).

Satisfactory results of treatment with sulphamezathine have recently been reported in the literature by Macartney et al (1942) and Morgan and Wylie-Smith (1943), also by Peters and Easby (1943), who reported one case of suppression of urine lasting one day in a child of two years, one case of transient haematuria and two cases of brawny oedema of the limbs; and by Jennings and Patterson (1942), who noted three children who developed rashes.

Dosage

The scheme of dosage which has been introduced recently is shown in table 4. The ' daily maintenance dose ' corresponds approximately to 1½ gr. per pound of expected body weight per day, for all ages up to 10 years when sulphapyridine or sulphadiazine are being used, and 2 gr. per pound of expected body weight per day, when sulphamezathine is being used. Sulphapyridine is given four-hourly; sulphadiazine and sulphamezathine six-hourly. The first two doses are double the estimated single dose and the second dose is given three hours after the initial dose, in all cases.

The scheme of dosage is somewhat higher than that usually advocated. As regards sulphamezathine, it was introduced solely on the clinical impression that smaller doses did not produce an early response. Unfortunately, owing to shortage of laboratory staff during the war, it was not possible until recently to check the blood sulphonamide levels These are now being carried out on patients receiving sulphamezathine orally in the above dosage and have shown a range of free sulphamezathine from 3·4 mgm. per cent. to 37 mgm. per cent. The higher figure occurred in a slightly dehydrated baby. The aim has been to produce a level of 10 mgm. per cent., though the optimum level has yet to be proved.

Using the same drug and similar dosage Jennings and Patterson (1942) found blood levels in 38 children ranging from 3·8 mgm. per cent. to 29·8 mgm. per cent. In a series reported from the Hospital for Sick Children, Great Ormond Street, by Hynes (1940), sulphapyridine was administered in doses estimated to produce a blood concentration of 4 mgm. per cent. Wide variations of blood levels in different children of the same weight and age were found. It is suggested, therefore, that the sulphonamide drugs can be used to the greatest advantage only if controlled by regular estimations of the concentrations in the blood.

Summary of conclusions

1. A comparison is made of two groups of children suffering from pneumonia, a pre-sulphonamide group of 100 cases and a sulphonamide group of 127 cases.

2. The total mortality rate in the first group was 18 per cent. and in the second group (sulphonamide treated) 9 per cent.

3. An attempt is made to evaluate the therapeutic effect of sulphapyridine, sulphadiazine and sulphamezathine by a comparison of percentage mortality, response to treatment, complications and toxic effects.

4. Sulphamezathine produced (a) the lowest mortality rate of 3·7 per cent. and (b) the quickest response to treatment—63 per cent. of cases were apyrexial and improving within two days and only 7·4 per cent. failed to respond within five days.

TABLE 4

SCHEME OF DOSAGE

Age	Sulphapyridine (4-hourly)		Sulphadiazine (6-hourly)		Sulphamezathine (6-hourly)	
	Daily maintenance dose	Single dose	Daily maintenance dose	Single dose	Daily maintenance dose	Single dose
0–18 months ..	*1½ gr. per lb. of expected body wt. per day.	—	*1½ gr. per lb. of expected body wt. per day.	—	*2 gr. per lb.of expected body wt. per day.	—
1½–3 years ..	2–3 gm.	½–½ gm.	2–3 gm.	½–¾ gm.	3–4 gm.	¾–1¼ gm.
3–5 years ..	3–4 gm.	½–¾ gm.	3–4 gm.	¾–1 gm.	4–6 gm.	1–1½ gm.
5–10 years ..	4–6 gm.	¾–1 gm.	4–6 gm.	1–1½ gm.	6–8 gm.	1½–2 gm.

(* For example, an infant of 15 lb. would receive 22·5 gr. of sulphapyridine or 30 gr. of sulphamezathine daily, i.e. 1·5 gm. and 2 gm. respectively. The initial dose of sulphapyridine would be 0·5 gm. followed by 0·5 gm. in three hours and then a maintenance dose of 0·25 gm. four hourly. For sulphamezathine 1 gm. followed by 1 gm. in 3 hours and then 0·5 gm. six-hourly.)

5. There was no significant variation in the incidence of complications with the three drugs used.

6. Sulphapyridine produced vomiting, rashes and renal complications in a few cases; sulphadiazine and sulphamezathine were not toxic in these patients.

7. A scheme of dosage is outlined which corresponds approximately to a ' daily maintenance dose ' for sulphapyridine and sulphadiazine of 1½ gr. per pound of expected body weight per day for all ages up to 10 years, and for sulphamezathine of 2 gr. per pound of expected body weight per day.

8. Estimation of the blood level of free sulphamezathine in recent cases showed a range from 3·4 mgm. per cent. to 37 mgm. per cent. The aim was to produce a level of 10 mgm. per cent. The optimum level is not yet established.

9. It is suggested that the sulphonamide drugs can be used to the greatest advantage only if controlled by regular estimations of the concentration in the blood.

Thanks are due to Dr. Donald Paterson for his encouragement and help in the preparation of this paper, to Dr. Janet Gimson for her help with dosage and to Miss Nora Hair for her patient assistance with case records.

References

Elliott, M. (1941). *Arch. Dis. Childh.*, **16,** 120.
Flippin, H. F., Schwartz, L., and Domm, A. H. (1943). *J. Amer. med. Ass.*, **121,** 230.
Hynes, M. (1940). *Lancet*, **1,** 261.
Jennings, P. A., and Patterson, W. H. (1942). *Ibid.*, **2,** 308.
King Lewis, F. L. (1944). *Ibid.*, **1,** 247.
Macartney, D. W., Luxton, R. W., Smith, G. S., Ramsey, W. A., and Goldman, J. (1942). *Ibid.*, **1,** 639.
Morgan, T. N., and Wylie-Smith, R. (1943). *Ibid.*, **2,** 731.
Peters, B. A., and Easby, M. L. (1943). *Brit. med. J.*, **2,** 230.

OBSERVATIONS ON OTITIS MEDIA AND MASTOIDITIS IN INFANCY

BY

EDWARD C. ROSS COUPER, M.D., F.R.F.P.S., D.P.H.

Deputy Medical Superintendent, Walton Hospital, Liverpool

There have recently been articles and correspondence in the medical journals regarding the relationship between mastoiditis and the diarrhoea and vomiting syndrome in infancy. It is thought that some observations, made mainly from a detailed investigation of a series of fifty infants suffering from this infection conducted a few years ago in Alder Hey Childrens' Hospital, on this important problem might be of interest. All the cases were thoroughly investigated to exclude other infections.

At the outset it must be emphasized that diarrhoea and vomiting are the two commonest signs of disease in infancy and that inflammation of the middle ear and mastoid antrum is only one of the many sources of parenteral infection which may give rise to them. In the recent articles and letters stress has been laid only on mastoiditis and it should be mentioned that otitis media alone may give rise to almost as serious an illness in an infant as the case which has progressed to mastoiditis. There is no doubt that these infections can cause serious illness, and it would seem that in some cases otitis media alone can be sufficient to produce a fatal issue.

Anatomy

There are one or two anatomical points which it is useful to keep in mind. The Eustachian tube is relatively wider and more horizontally placed than in the adult (Leathart, 1943). The infantile tympanic membrane lies at a much more acute angle and may be almost horizontal (Lyman, 1927a). This accounts to some extent for the difficulty in examining the tympanic membrane, the object surveyed appearing oval rather than circular. At birth a soft mesodermal embryonic tissue, which presents a myxomatous appearance on section, fills the antrum, attic and upper portion of the middle ear and facilitates the spread of infection (Lyman, 1927a; Marriott, 1925a and b). It is said that this embryonic tissue also lines the inner aspect of the tympanic membrane rendering it thicker and explaining the infrequency of spontaneous perforation in the infant (Le Mée, 1936). Lyman (1927a) suggested that in cases in which the gastro-intestinal symptoms improve with myringotomy alone, the infection is confined to the lower part of the middle ear cavity and that when infection has spread to the upper part with its embryonic tissue myringotomy does not provide sufficient drainage. Inflammation and swelling of this tissue hampers adequate drainage. Fig. 1, which is a microphotograph of a normal infantile mastoid, shows this tissue filling one of the air cells.

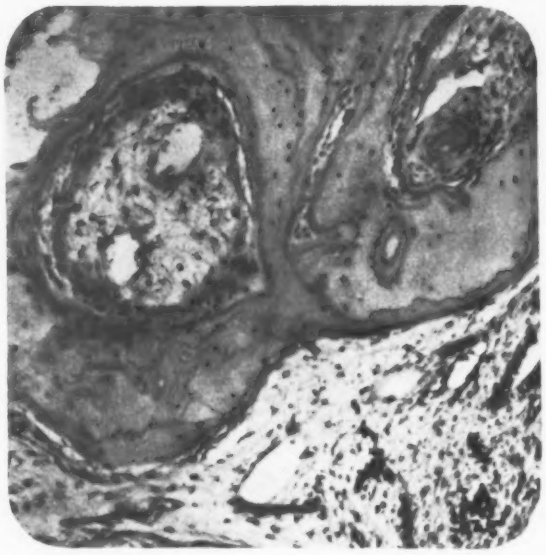


FIG. 1.

Bacteriology and pathology

Swabs were taken from all cases with otorrhoea and after myringotomy, and from the nasopharynx of all infants. Cultures from these swabs invariably produced a mixed growth and in nearly all staphylococci predominated, particularly in the ear swabs. Swabs were taken at operation and in the post-mortem room with similar results. The results of this part of the investigation lead to no satisfactory conclusion. Blood cultures proved negative with one exception, in which a haemolytic staphylococcus was obtained. In 64 per cent. of the families a history of recent respiratory infection was found, e.g. 'colds,' sore throat, bronchitis, pneumonia and influenza, and a recent leading article in the British Medical Journal (1943) has raised the question of staphylococcal pneumonia. Recently several infants have been observed suffering from staphylococcal pneumonia and it is possible that the staphylococcus has some pathogenic significance in otitis

media and mastoiditis. Certain staphylococci are known to elaborate an enterotoxin but what part, if any, this plays in producing the gastrointestinal symptoms is pure conjecture. Many attempts have been made to establish a satisfactory bacteriology

FIG. 2.

without convincing result, the commonest organisms found being staphylococci and streptococci. Alden (1927) found haemolytic streptococci in the ' latent ' type of mastoiditis whilst Spahr (1929) found staphylococci the commonest organisms in cultures from the middle ear. Marriott (1925a) stresses the importance of haemolytic streptococcal infection of the mastoid antra in his cases; Smith (1924) and Holsclaw et alia (1930), also found them the commonest organisms. Fig. 2 shows a section of an infected mastoid process in which many pus cells can be seen in the embryonic tissue occupying the air cells. In fig. 3 the section appears to cut the tip of an air cell but pus cells can be seen in the bony wall.

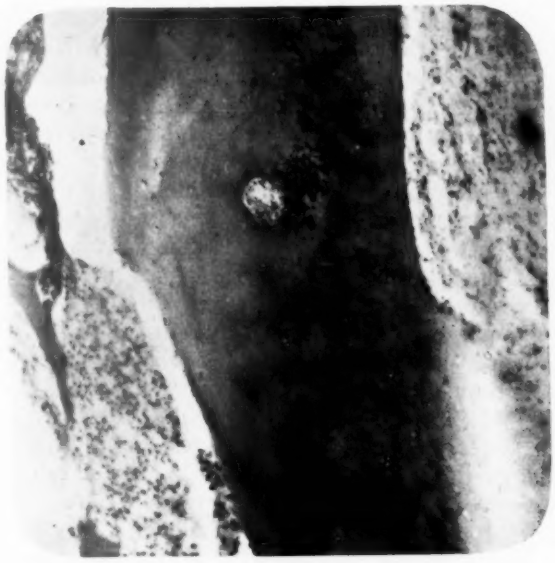


FIG. 3.

Etiology

It seems likely that the majority of these infections result from upper respiratory infection derived from those in attendance. As Leathart (1941) points out the anatomical peculiarities of the Eustachian tube lend themselves to infected mucus and discharges making their way into the middle ear and setting up an otitis followed in certain cases by mastoiditis. It is possible that infected milk may have a similar effect although no fluid recognizable as milk has been noted in the middle ear at post-mortem examination. Once the infection has begun, the embryonic tissue already mentioned assists the spread of the infection. Dean (1927a and b) stressed the importance of paranasal sinus disease in producing a clinical picture of gastro-enteritis and suggested that aural infection and paranasal sinus disease may coexist—a pansinusitis. If this is so, it may explain failure of treatment directed against aural infection alone. As in all infections of infancy, bottle-fed infants are more likely to develop aural infection. In the series investigated the great majority had less than three months of breast feeding. Only two were entirely breast fed and only three had more than three months. The subsequent bottle feeding was fairly satisfactory but the supply of vitamins was most unsatisfactory. Seventeen cases had no vitamins at all.

Incidence

Aural infection can occur in any infant, the youngest case noted being only five days old. In 1324 infants under one year (McConkey and Couper, 1938) it was found that 195 (14 per cent.) had suffered from aural infection. Of the 195 cases, 116 were associated with other conditions, e.g. respiratory infections, athrepsia, nasopharyngitis. In seventy-two cases aural infection was the only detectable disease and seven cases presented the ordinary classical signs of acute mastoiditis. Cooper found that otitis media was by far the commonest parenteral infection, occurring in 26 per cent. of his cases, while Ebbs (1937) found otitis media in 61 per cent. of infants dying in the first year of life. The view (Leathart, 1941), based on calculation from a series of 72 post-mortems among whom 59.6 per cent. were found to have mastoiditis, that, of 30,000 infants dying annually from gastro-enteritis 18,000 suffer from mastoiditis and that 14,400 of these could be saved by operative interference, is not in keeping with the experience of the present writer.

Signs

(1) GENERAL. The commonest signs in order of frequency are diarrhoea, vomiting, loss of weight and restlessness. If the diarrhoea and vomiting are severe then the infant is in danger of becoming dehydrated and toxic. The onset of dehydration is an occurrence of the greatest importance as it has a

bearing on the treatment to be described later. In fact, cases of aural infection can conveniently be divided into two groups—those which are dehydrated and those which are not. It is interesting that the incidence of otorrhoea is higher in the non-dehydrated cases than in the dehydrated cases. In 39 non-dehydrated cases (McConkey and Couper, 1938) 33.3 per cent. had otorrhoea on admission to hospital while in 33 dehydrated cases only 9 per cent. had otorrhoea. This suggests that adequate drainage has a bearing on the development of dehydration and toxicity. When efficient drainage from the middle ear in cases of otitis media can be maintained by myringotomy, repeated if necessary, dehydration does not supervene. When drainage is difficult to maintain and dehydration occurs probably a proportion of cases have developed mastoiditis. On the other hand, in cases in which copious discharge has persisted for four weeks or longer with the child in good condition, mastoiditis has also probably developed. The temperature chart has not been found to be of much assistance but on the whole fever is higher in the dehydrated toxic cases than in those not so affected.

(2) LOCAL. Examination of the tympanic membrane will frequently lead to the detection of this source of parenteral infection. The appearances of the membrane vary greatly. In some cases it is acutely inflamed, red and bulging or only mildly injected. In some cases it merely lacks the normal lustre, while in others it is apparently normal. The highest percentage of obviously pathological drums is found in the dehydrated toxic patients. Sometimes in these cases an apparently normal drum has pus behind it and the infant may also have mastoiditis. Sometimes myringotomy may be performed without apparent result, but when dehydration is overcome discharge commences. Alden (1927) explained the absence of signs in the tympanic membrane by the fact that the infant's Eustachian tube is shorter and wider than the adult's and drainage can take place more easily by this route. In other cases small unnoticed amounts of discharge may be detected by aural examination. Some parents seem to regard a little aural discharge as a normal occurrence and the dangers of this theory should be thoroughly explained.

There are two types of infantile mastoiditis. In the 'latent' type none of the ordinary signs is present. There is no swelling, redness, or oedema over the mastoid process, which renders the diagnosis extremely difficult. Leathart (1943) sets great store by enlargement of glands in the posterior triangle of the neck. Unfortunately there are other causes of such enlargement and it has not been possible to confirm the value of this sign. The second type is the ordinary classical mastoiditis which presents the usual signs of redness, oedema, and forward displacement of the pinna. The latter type is unfortunately much rarer than the former and the infant never becomes dehydrated. Having regard to the frequent bilateral occurrence of aural infection in infancy the possibility of a 'latent' mastoiditis on the other side should be kept in mind. One such case has been observed and the 'latent' mastoiditis ultimately lead to a fatal result.

Diagnosis

Examination of the tympanic membrane, without which no examination of an infant is complete, is of the greatest importance and may lead to the real cause of gastro-intestinal signs being discovered. Provided an electric auroscope with a small speculum is used it is always possible to examine the drum except in very small infants such as premature infants. The difficulty lies in the interpretation of the findings and this is a matter of experience. The most difficult drums, fortunately not many, are those which appear normal, and these may quite reasonably be missed. The more obvious degrees of inflammation are quite easily detected. Both tympanic membranes should always be inspected and if one ear is already discharging at the time of the examination, the ear without discharge should obviously be examined first in order not to convey infection to a possibly healthy ear.

The diagnosis of the classical type of mastoiditis is fairly easy, but when attention is directed to the ear by changes in the tympanic membrane, the diagnosis of the 'latent' type presents a very difficult problem. The diagnosis can best be made by considering the general condition of the infant, particularly the progress of its weight curve, the severity and duration of the illness, the duration of aural discharge, the presence of changes in the tympanic membrane and response to treatment. A sudden drop in weight is suggestive of parenteral infection of this type.

Treatment

It is not proposed to deal with the treatment of dehydration and only the treatment of aural infection will be considered. On the whole such treatment should be as conservative as possible.

(1) LOCAL MEDICATION. For acutely inflamed drums before and after discharge has commenced, instillation of 'glycerin and carbolic' drops is useful. Later as the acute phase passes spirit drops may be employed with benefit.

(2) MYRINGOTOMY. This minor operation is easy to perform and in some cases can be almost a life saving measure. No anaesthetic is necessary and the operation is best performed through the speculum of an electric auroscope. The anatomy previously described should be kept in mind. The difficulty lies in recognizing when to perform the operation. This is a matter of correct interpretation of the signs seen in the drum. When the drum is acutely inflamed and bulging, the decision is easily made but many much less pathological drums have been opened and pus released. A single myringotomy is sometimes sufficient and the general condition and gastro-intestinal symptoms improve. After a successful myringotomy the drum should be

inspected daily because in the infant the opening seems to be peculiarly prone to seal over rapidly, thus preventing discharge of pus. In some cases maintenance of drainage is difficult and several myringotomies may be necessary before the infection is overcome. Note of aural discharge should be made on the weight chart. If this is done it will be noticed that if discharge ceases before the infection is overcome the infant either fails to gain or actually loses weight. On the other hand, if discharge ceases and the infant is gaining weight satisfactorily it is probable that infection has been overcome. In the former case a further myringotomy may be necessary perhaps in the same drum or the other drum. As in all infantile diseases the weight curve is an extremely useful guide to the success or otherwise of treatment. One explanation has been offered for the unfruitful myringotomy, and spontaneous drainage via the Eustachian tube is another suggested explanation (Alden, 1927).

(3) SURGICAL DRAINAGE OF THE MASTOID ANTRUM. In the classical case the decision is easy and operation is the treatment of choice. In the 'latent' type the decision to operate is an extremely difficult one. The factor which should influence this decision most is the presence or absence of dehydration. In my opinion, operation, if indicated, may be risked in the mildly dehydrated infant but in the severely dehydrated, toxic child operation should never be undertaken. If, however, severe dehydration can be overcome by the usual methods and the infant's general condition improved then operation may be carried out with much greater safety if indicated. The type of case in which good operative results may be obtained is that in which the aural infection has become more chronic with three or four weeks otorrhoea and the infant's general condition is good. It is felt that this decision is one which should remain in the hands of the paediatrician as the most dire result of aural infection, namely the onset of dehydration and toxicity, is a paediatric problem and the paediatrician is best able to say when the infant is fit for operation.

The published results are interesting.

Author	No. of operations	Alive	Dead	Percentage recovery
Byfeild (1918) ..	6	6	0	100
Renaud (1921) ..	10	1	9	10
Lyman and Alden (1925)	15	8	7	53
Lyman (1927a) ..	30	22	8	73
Mitchell, et al. (1929)	16	7	9	43
Wishart (1930) ..	13	1	12	7
Holsclaw (1930) ..	16	8	8	50
Carmack (1930) ..	28	20	8	71
Findlay (1932) ..	9	2	7	22
Morris and Smith (1932)	6	5	1	83
Maizels (1934) ..	10	5	5	50
Leathart (1941) ..	150	120	30	80
Author's cases—				
Dehydrated ..	16	2	14	12
Non-dehydrated ..	10	10	0	100

The majority show a recovery rate of over 50 per cent. My cases are divided into two groups, and it can easily be seen in which group the best results are obtained. Carmack (1930) is of the opinion that operation should never be carried out in the acute phase of the illness, and it was found (McConkey and Couper, 1938) that 80 per cent. of dehydrated cases which were operated upon died and that 86 per cent. of such cases treated conservatively died. Surgical drainage of the mastoid antrum in severely ill infants without some local indication, 'a shot in the dark,' is unsound. Many such cases have come to the post-mortem room when it has been demonstrated quite clearly that operation would have been of no avail.

(4) SULPHONAMIDES. More recently treatment of acute otitis media with sulphadiazine has been attempted. At present the series is too small to allow of conclusions being drawn, but it would seem that, in cases with an acutely inflamed drum and no discharge, sulphadiazine in full doses causes rapid improvement. It is advisable to continue the drug, which is very well tolerated, for about a week, otherwise relapses may occur. On the other hand, once otorrhoea has commenced the exhibition of sulphadiazine appears to exert no beneficial effect. The explanation of this is not clear. Possibly after otorrhoea has begun the infection becomes a mixed one and therefore less amenable to the drug.

Prophylaxis

(1) INFECTION. Persons suffering from colds and sore throats should on no account come into contact with infants. Attendants, nurses and doctors should invariably wear masks. Mothers seem reluctant to wear masks even when the reason has been explained. Nevertheless facilities should be available, e.g. a supply of masks at clinics, so that mothers can wear masks even at home on the slightest suspicion of respiratory infection. Demonstrative fondling and kissing of infants by relatives and friends cannot be too strongly deprecated.

(2) POSITION. For reasons already given, very weakly and ill infants should as far as possible be nursed in a position approximating to Fowler's position.

(3) FEEDING. Infants should always be fed in a semi-upright position and when bottle fed should if possible be taken out of the cot to be fed. Bottles should never be left in the cot beside a recumbent infant.

(4) ISOLATION. In hospitals and institutions infants should always be nursed according to a strict barrier nursing technique with gowns and masks. This should be a routine and not merely introduced when some epidemic occurs. The ideal system is of course cubicle wards, but it is possible to carry out the technique efficiently in an open ward provided overcrowding is avoided. Difficulty arises when the mothers have to come into contact with their infants, and they ought to be instructed in carrying out the technique.

Post-mortem examinations

Many autopsies have been performed and the following are the noteworthy features.

(1) The almost invariable bilateral occurrence of infection of the mastoid antra.

(2) The absence of intracranial complications, such as sinus thrombosis and intracranial abscess found in older patients.

(3) The absence of intestinal lesions sufficiently gross to account for the extreme illness of these infants.

(4) In certain cases the impression was gained of a severe toxaemic or septicaemic state, although the latter view is not supported by the results of blood culture.

Summary

Eclampsia has been described as the 'disease of theories.' Aural infection in infancy might well be described as the 'disease of problems.'

(1) Can aural infection be an adequate explanation of gastro-intestinal signs? In my opinion a certain proportion of such cases can be so explained although this view has not gained widespread acceptance.

(2) The bacteriological investigations so far published are unsatisfactory. A suggestion has been made regarding the pathogenicity of the staphylococcus and perhaps further investigation would be fruitful.

(3) The difficulty of diagnosis in 'latent' mastoitditis has been described. How can the diagnosis be made in the absence of satisfactory local signs?

(4) In hospital the problem of infection can be largely overcome, but outside it is a different matter and is really a sociological problem. Overcrowding and bad housing must exert a great influence on the spread of infection.

(5) Breast feeding should be encouraged in every possible way. Some mothers seem disinclined to breast feed their infants, especially in the present difficult circumstances.

Thanks are due to Dr. W. E. Crosbie, Medical Superintendent, Alder Hey Childrens' Hospital, Liverpool, for permission to publish these results.

References

Alden, A. M. (1927). *Arch. Otol.*, **5,** 39.
Brit. med. J., 1943, **2,** 783.
Byfeild, A. H. (1918). *J. Amer. med. Ass.*, **71,** 511.
Carmack, J. W. (1930). *Ann. Otol. etc., St. Louis*, 39, 75.
Cooper, E. D. (1937). *Arch. Dis. Childh.*, **12,** 339.
Dean, L. W. (1927a). *Ann. Otol. etc., St. Louis*, **36,** 933.
—— (1927b). *Arch. Otol.*, **6,** 201.
Ebbs, J. H. (1937). *Proc. roy. Soc. Med.*, **30,** 49.
Findlay, L. (1932). *Arch. Dis. Childh.*, **7,** 307.
Holsclaw, F. M., Boehm, C. A., and Bierman, J. M. (1930). *Amer. J. Dis. Child.*, **39,** 747.
Leathart, P. W. (1941). *J. Laryng.*, **41,** 320.
—— (1943). *Brit. med. J.*, **2,** 168.
Le Mée, J. M. (1936). *Bull. Soc. Pédiat. Paris*, **34,** 33.
Lyman, H. W. and Alden, A. M. (1925). *Laryngoscope*, **35,** 586.
Lyman, H. W. (1927a). *Arch. Otol.*, **6,** 526.
—— (1927b). *Ann. Otol. etc., St. Louis*, **36,** 903.
Maizels, M. (1934). *Lancet*, **1,** 1329.
Marriott, McK. (1925a). *Amer. J. Dis. Child.*, **30,** 577.
—— (1925b). *Laryngoscope*, **35,** 592.
Mitchell, A. G., McCarthy, M. F., Leichliter, J. W., and Seinsheimer, F. (1929). *J. Amer. med. Ass.*, **92,** 970.
Morris, M., and Smith, W. B. (1932). *Amer. J. Dis. Child.*, **44,** 964.
McConkey, G., and Couper, E. C. R. (1938). *Arch. Dis. Childh.*, **13,** 137.
Renaud, M. (1921). *Bull. Soc. méd. Hôp. Paris*, **45,** 1326.
Smith, D. T. (1924). *Amer. Jour. Dis. Child.*, **28,** 1.
Spahr, M. B. (1929). *Ibid.*, **37,** 541.
Wishart, D. E. S. (1930). *J. Amer. med. Ass.*, **95,** 1084.

CASE REPORTS

CONGENITAL ATRESIA OF THE OESOPHAGUS

AN ATTEMPT AT SURGICAL TREATMENT

BY

J. N. O'REILLY, D.M., M.R.C.P.,
Paediatrician, St. Helier Hospital, Carshalton;

R. H. FRANKLIN, F.R.C.S.
Surgeon, E.M.S., Department of Surgery, British Post-Graduate Medical School, Hammersmith;

and

M. D. DALEY, M.D., M.R.C.O.G.,
Assistant Obstetrician, St. Helier Hospital, Carshalton.

The commonest congenital abnormality of the oesophagus is atresia of the upper third, the lower two-thirds springing from the trachea at its bifurcation or from the right bronchus. So far no successful treatment had been devised, but experience with a case gave some hope that the difficulties can be overcome.

An infant weighing 4 lb. 3 oz. was born at the thirty-sixth week of pregnancy on Oct. 31, 1943. It was placed in the premature nursery in an oxygen tent and, according to the usual practice of the hospital, was disturbed only for changing during the first twenty-four hours. The baby seemed lively and cried well. Next day it was given its first feed of one drachm of glucose saline. This was vomited and the child became slightly cyanosed. Successive 2-hourly feeds were vomited, and on a few occasions the child went blue. Feeds were accordingly stopped and the baby was given subcutaneous saline 20 c.c. by syringe. After some hours a further feed was attempted with the same results. An abnormality of the oesophagus was now suspected and appeared to be confirmed by the failure of an attempt to pass a catheter for gavage. Feeds were suspended and subcutaneous saline resumed 4-hourly. On Nov. 2, lipiodol 2 c.c. was put into the oesophagus by tube over the tongue and x-ray confirmed the presence of a blind sac. The baby had passed no meconium, so that it was felt necessary to run lipiodol into the rectum to exclude the presence of atresia of the colon. The colon appeared quite normal and the injection caused the evacuation of meconium. The baby stood the manipulation very well. No evidence of aspiration pneumonia had so far been discovered, and it was decided that an effort should be made to reconstitute the oesophagus. On the evening of Nov. 2 when the infant was 72 hours old, the following operation was performed:

Operation. Local anaesthesia (procaine 1 per cent.). With the infant lying on the left side and with the right arm drawn well forwards, an incision was made from near the midline in front to the angles of the ribs behind. This incision was made over the intercostal space just below the angle of the scapula. The pleural cavity was opened and a mastoid retractor introduced to hold the ribs apart. The right lung collapsed and did not appear to have undergone pneumonic consolidation.

A good exposure of the oesophagus was obtained. The upper portion ended as a blind sac at the level of the vena azygos arch. The lower portion of the oesophagus was half the diameter of the upper portion and, passing upwards from the stomach, rapidly narrowed at the level of the azygos arch and entered the termination of the trachea. It was apparent that division of the azygos arch would facilitate further procedures and this was carried out between two catgut ligatures passed with an aneurysm needle. Particular attention was paid to the condition of the infant during this procedure and no untoward effects were noticed. The upper end of the lower portion of the oesophagus could now be seen more clearly passing to the inner side of the upper blind sac and communicating with the trachea at about its bifurcation. The arrangement of the parts was seen to conform to what is commonly found in these cases; a favourable feature was the close approximation between the upper and lower portions of the oesophagus. The decision was made to tie off the tracheal fistula and attempt a direct restoration of the oesophagus as had been done in a previous unreported case in which the infant died some 17 hours after operation. The condition of the infant improved somewhat after the tracheal fistula had been tied off.

The parts to be anastomosed were controlled with stay sutures. The anastomosis was effected by making a vertical incision in each portion of the oesophagus and suturing them together transversely. Two mattress sutures were used to approximate the parts, and the anastomosis was completed by a running through and through suture. After completing the first half of the anastomosis, a nasal catheter was passed through the mouth and down into the stomach—this step greatly facilitated the completion of the anastomosis. No. 75 linen thread was used throughout for the anastomosis.

Sulphanilamide powder was sprinkled around the anastomosis and the chest closed without drainage. A little air was aspirated from the pleural cavity after the chest wound had been closed. The operation lasted for an hour and did not appear to have produced any deterioration in the infant's condition.

After-treatment. (Nov. 2.) The child was returned to the premature nursery and placed in an oxygen tent. The oesophageal catheter was left in position and 2 drachms of glucose water were given through it without difficulty. Thereafter feeds of expressed breast milk (E.B.M.) and glucose water (G.W.) in equal parts, 3 drachms were given 2-hourly.

Nov. 3. The baby's condition was poor. It was jaundiced and pale. The temperature was 105° F., with rapid respiration. This was apparently due to overheating in the oxygen tent which was an improvized apparatus, and the child improved rapidly when taken out of the tent. Feeds of 3 drachms of E.B.M. were given 2-hourly and, as the child appeared a little dehydrated, two subcutaneous injections of 40 c.c. normal saline were given in the day.

Nov. 4. Condition fair. Tube feeds continued but respiration became progressively more laboured during the day. Expiration seemed difficult. Hyperextension of spine eased matters. T. 101° F.; bowels open twice, once with meconium and once with brownish motion; forty-eight hours after operation it was decided to remove the oesophageal tube. The child immediately took 2 drachms of E.B.M. from a feeder and went to sleep. Two hours later the chest was examined and found to be moving fairly well, the left side showing better expansion than the right. It took 2 drachms of feed well and then refused. Two hours later it again refused its feed and became cyanosed. The colour was poor and the breathing difficult. Mouth feeding was stopped and subcutaneous drip saline infusion was started.

Nov. 5. Condition poor with laboured respiration. Fontanelle sunken; breathing stopped once during the morning. It was decided to find out if the oesophagus was patent; 2 c.c. of lipiodol were injected. Respiration ceased and the child almost died. Aspiration with a mucus catheter produced some oil and—more important—thick mucus from the pharynx. Respiration restarted and became regular and much easier than previously. The picture taken showed that the lipiodol had passed successfully down the oesophagus, but that some had been aspirated into the lungs (fig. 1). Moist sounds were audible over both lung fields. The aspiration of mucus was repeated every two hours, with the result that the previously laboured breathing entirely disappeared and the moist sounds also cleared up. Attempts at mouth-feeding had to be abandoned, however, on account of inability to swallow. Saline infusions were continued.

Nov. 6. General condition fairly good, but the legs became oedematous following salines. In the afternoon oesophageal feeds were started, the tube being passed 4¾ inches from the line of the gums. In spite of some misadventures due to attacks of cyanosis this method of feeding was successful, the food being E.B.M. fortified with soluble calcium caseinate. The aspiration of mucus was continued every two hours. The respiration remained fairly satisfactory after the feeds and quite good between feeds. A rectal saline was also given and retained.

Nov. 7. General condition much improved. Taking feeds well without misadventure. Passed a normal yellow motion. The baby had its best day since operation.

Nov. 8. During night respirations increased in rate and became shallow and grunting in character. T. 104° F. The feeds were taken fairly well until 7 a.m., but the colour was less good. Mucus extraction and oxygen improved things, but the child was clearly very ill. Its condition deteriorated

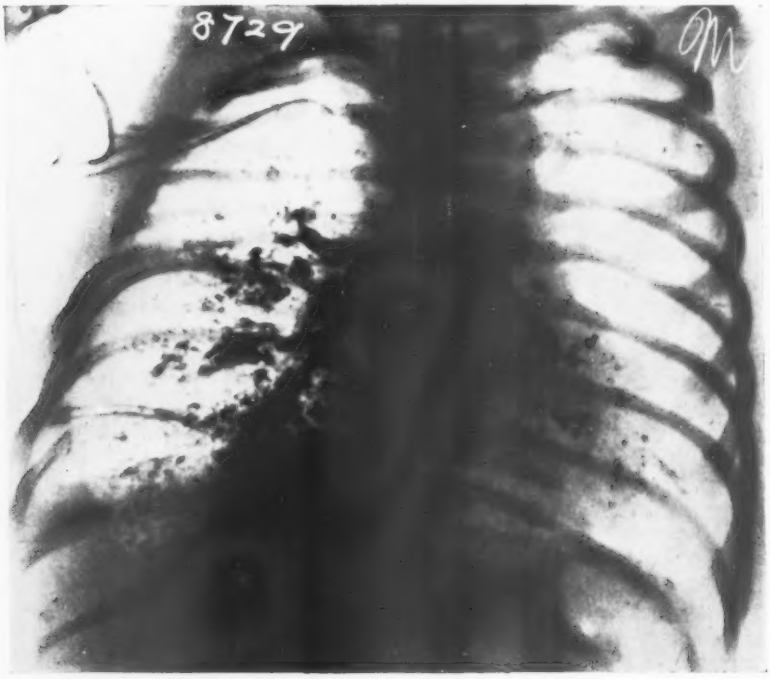


FIG. 1.

FIG. 2.—Arrow points to the leak in the reconstructed oesophagus.

and it died about midday, having survived operation for over 5½ days.

A post-mortem examination was performed. The operation scar was found closed, but there was evidence of low-grade infection around the sutures and under the skin. The sutures closing the thoracic wall were intact, but again there was evidence of damage by sepsis to the parietal pleura immediately underlying each stitch.

On removing the sternum and opening the right pleural cavity about 1 oz. of greenish purulent fluid escaped. The right lung was comparatively well expanded and there was no evidence of any residual air in the pleural cavity. On retracting the right lung forwards as at operation, it was found that one of the sutures holding the oesophageal anastomosis had given way and that some milk curd was exuding through the aperture into the right pleural sac. There was evidence of sharp inflammatory reaction around this leak and the lung was already becoming bound to the parietes in an effort to wall it off. While the thoracic viscera were being dissected away from the vertebral column, more oesophageal contents were pushed through the gap, and in spite of the utmost care in handling, another suture gave way. Examination showed that the stitch holes were septic and were very frail. Section through the suture line revealed that there had been little attempt at healing. The heart appeared quite normal.

The lungs did not appear grossly abnormal. On section, apart from congestion, there was little abnormality.

The abdominal viscera showed no abnormality, but the stomach was very much of the ' inverted retort ' shape commonly seen in the young baby. No other abnormalities were found. Fig. 2 shows the post-mortem specimen.

Comment

Attempts at reconstitution of these cases of congenital atresia of the oesophagus have been made previously, but complete success has yet to be obtained. This case was most instructive for several reasons which may be summarized as follows:—

(1) The incidence of the abnormality is probably somewhat greater than is realized. This case is the third diagnosed by one of us (J. N. O'R.), within twelve months. Two other previous cases have been operated upon by another (R. H. F.).

(2) It has been shown that a new-born and even

premature baby can survive the severe operative procedure involved.

(3) Early diagnosis, planned operation and careful after-treatment are essential. There must be the closest co-operation between the obstetrician, the paediatrician and the surgeon.

(4) The problem of the post-operative feeding is perhaps the most difficult one to solve. It is concluded that mouth-feeding should be avoided in a future case. The oesophageal tube cannot be kept clean and its presence caused such trauma in the pharynx as prevented swallowing after its withdrawal, and gave rise to the mucous secretion which so greatly impeded breathing. Gastrostomy is probably the method of choice, but is difficult to be dogmatic about the time at which it should be performed. It is suggested that twenty-four hours after the thoracotomy is the optimum time, the oesophageal tube being left in place until this time.

(5) It will be unnecessary in a future case to subject the child to the stress of a lipiodol x-ray which nearly proved fatal on the third day after operation. The reconstructed oesophagus has been shown to be an effective passage.

Thanks are due to Dr. J. Ferguson, County Medical Officer for Surrey, and Dr. E. B. Brooke, Medical Superintendent of St. Helier Hospital, for permission to publish this case.

GIANT CONGENITAL DIVERTICULA AND NEONATAL RUPTURE OF COLON: A CASE ASSOCIATED WITH TRUE CONGENITAL PARTIAL HYPERTROPHY OF THE CROSSED TYPE

BY

J. EDGAR MORISON, M.D., B.Sc.

(From the Department of Pathology, Queen's University, Belfast, N. Ireland)

True diverticula of the colon are of considerable morphological interest and the occurrence in a new-born child of two large cystic diverticula in the pelvic colon, and the rupture of the bowel opposite one of them, appears unique and capable of providing some information as to their significance.

Case record

Clinical history. The patient died on the twelfth day of life, having been delivered by a Caesarian operation for disproportion. He was difficult to resuscitate at birth and the abdomen always appeared distended. This distension varied somewhat, but there were no other unusual symptoms until he suddenly collapsed and died in two hours.

Post-mortem examination. The body was that of a well-nourished male infant. The left side of the cranium and face, especially the mandible and ear, was larger than the right. This asymmetry was less marked posteriorly. No certain difference could be detected in the arms, thorax or abdomen, but the left leg was 2 cm. shorter than the right and this was largely accounted for by the shortening of the femur. The thickness of the thigh was proportionately altered, but asymmetry of the feet was not detected. On opening the cranium the left anterior and middle fossae of the skull were obviously larger than the right, but the disporportion between the posterior fossae was less certain. The cerebral convolutions were normal, but the cerebrum and even the cerebellum and pons shared in the asymmetry of the skull. No asymmetry of the thoracic or abdominal organs was demonstrable.

Except for the pelvic colon the contents of the thorax and abdomen were normal. The colon had a long free mesentery and lying in it, and slightly behind the bowel and almost 7 cm. from the anus, there was a cystic cavity 4 cm. from side to side, 3·5 cm. from above downwards and 2 cm. from front to back (fig. 1). This communicated with the lumen of the bowel by an orifice 1·2 cm. by 0·5 cm. in diameter. Its walls were 2 to 3 mm. thick, but showed no condensation of muscle into bands. Beginning 4·5 cm. above this opening and extending for 3·0 cm. the mesenteric wall of the bowel was expanded into a similar cavity with thick walls. Both diverticula received their blood supply from the arcade of the inferior mesenteric artery. The superior cavity extended 1·0 cm. above and 1·5 cm. below its wide entrance, and when it was dilated the part below the opening was capable of compressing the adjacent bowel and producing obstruction. Immediately opposite this upper aneurysmal like swelling the anti-mesenteric wall of the bowel was thinned out over three localized areas. These were 3 to 6 mm. in diameter, they did not bulge outwards, but through the largest a small perforation had occurred.

FIG. 1.—The two diverticula in the mesentery of the long pelvic colon. ¾ natural size.

Histological examination. Sections from the wall of the diverticula showed greatly hypertrophied

smooth muscle. There was some attempt at an arrangement of this into two layers with large prominent nerve cells between them, but often the layers intermingled. The lining consisted of acini of mucus producing cells, and deep to these a few small aggregates of lymphocytes and a well-defined layer of submucous muscle. Sections through the thin areas in the wall opposite the upper diverticulum showed the defect to consist of a relatively abrupt disappearance of both muscle layers (fig. 2). The

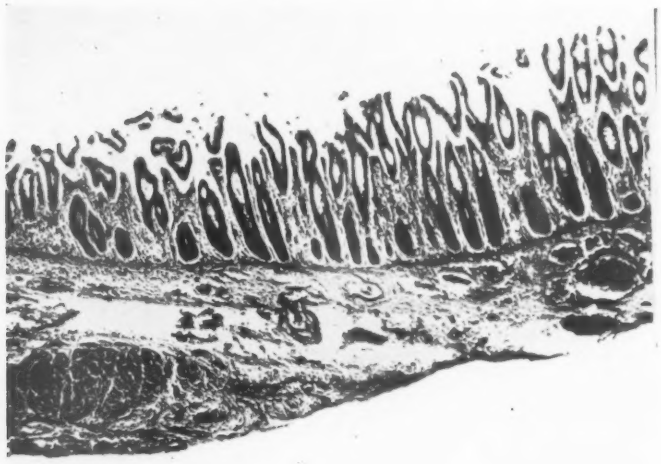


FIG. 2.—The longitudinal and circular muscle are deficient and the submucosa lies next the serosa near the site of the rupture. ×34.

submucous muscle was preserved and the mucous glands did not penetrate more deeply than normal, but there was a rather diffuse increase in lymphoid tissue. There were small aggregates of polymorphs and patches of necrosis in the oedematous wall near these defects and some fibrin lay in the wall and on the serosal surfaces.

A complete histological examination of the other organs revealed little of relevant interest and the final anatomical summary read:—

Two true giant diverticula mesenteric border of pelvic colon. Focal areas of congenital absence of muscle opposite upper diverticulum. Perforation. Generalized peritonitis. True congenital partial hypertrophy of crossed type. Congenital patency of interventricular septum. Gross aspiration of liquor amnii. Patchy atelectasis.

Discussion

An early explanation offered by Roth (1881) for true congenital diverticula was that they represented a Meckel's diverticulum. Some diverticula may originate in this way, and even a diverticulum lying within the layers of the mesentery might be explained by abnormal fixation early in growth. The theory is difficult to accept when a diverticulum lies below the caecum or when there are several diverticula.

Lewis and Thyng (1907–8) described in pig, rabbit and human embryos, chiefly of 5·5 to 32 mm. size, proliferations of the epithelial cells of the gut forming small cystic aggregates isolated from the lumen or communicating with it. Later many of these again become incorporated in the lumen, but some may come to lie in the wall of the intestine or outside it. Diverticula retain a communication with the lumen, while aggregates remaining isolated from the lumen form enterogenous cysts. Response to pathological stimuli or the proliferation of heterotopic epithelium explains any difference in the epithelium from that in the gut. This theory is elaborated with many illustrations by Evans (1929–30). It is best able to explain the present case. However, only in one embryo is there a record of such an epithelial proliferation in the large intestine, and that was near the caecum in a 32 mm. pig embryo. There are correspondingly very few reports of diverticula or cysts in the large bowel though the case described by Wright (1919–20) of a large diverticulum in the mesosigmoid of an adult may be compared with the present one.

Boikan (1930) in a discussion of meconium peritonitis and rupture of the gut in the newborn, in the absence of strangulation, cysts or diverticula, emphasized the occurrence of defects in the muscle associated with localized proliferation of lymphoid tissue and with a deeper penetration of mucous gland acini into the wall than usual. Lattes (1943) also emphasized lymphoid hyperplasia and abnormally deep glands in the ileum in a case of foetal perforation with pseudomyxoma peritonei. Boikan believed that the epithelial proliferations described by Lewis and Thyng determined a localized proliferation of lymphoid cells with disappearance of muscle elements. In the present case there was slight prominence of lymphoid cells, but no anomaly of the mucosa or of the submucosal muscle at the site of the defect. There may have been considerable disturbance in the development of the muscle adjacent to the large diverticulum from some other cause. It is important, however, to recognize that post-natal rupture of the bowel or pre-natal meconium peritonitis may result from some such localized defect in the muscle of the wall. Experimentally it is difficult to rupture the bowel of normal infants at post mortem. Unless there is interference with the blood supply from strangulation some such defect,

however brought about, must be excluded before trauma is considered. It will often be masked by the early onset of post-mortem necrosis.

True hypertrophy is distinguished from false by the involvement of the bones and the classification is discussed by Stoesser (1928). A congenital partial hemihypertrophy involves a part of one side only. But if, for example, an arm on one side and a leg on the other are involved the condition is described as a congenital partial hypertrophy of the crossed type. The present case belongs to this group as did six of the thirty cases of partial hypertrophy reviewed by Gesell (1921). In some cases the whole of one side including the paired viscera is involved and the condition is described as a total hemihypertrophy. Gesell endeavours to interpret cases of hemihypertrophy as examples of asymmetry due to deviation in the normal process of twinning at an early stage. The possibility of incomplete twinning with duplicity of only one organ is sometimes advanced as a basis for intestinal tract anomalies (Bland-Sutton, 1919–20; Edwards, 1929–30). No such considerations appear relevant to the present case where there are two distinct diverticula, nor does any theory of twinning adequately explain cases of the crossed type of hypertrophy.

Summary

Two large cystic diverticula occurred in the pelvic colon of a twelve-day old infant and perforation occurred through a muscle defect opposite the upper one. These findings and an associated true congenital partial hypertrophy of the crossed type are discussed.

Thanks are due to Mr. H. C. Lowry for permission to record this case, to Professor J. H. Biggart for his advice and to Mr. D. McA. Mehaffey for the photographs.

REFERENCES

Bland-Sutton, J. (1919–20). *Proc. roy. Soc. Med.*, **13,** 128.
Boikan, W. S. (1930). *Arch. Path.*, **9,** 1164.
Edwards, H. (1929–30). *Brit. J. Surg.*, **17,** 7.
Evans, A. (1929–30). *Loc. cit.*, 34.
Gesell, A. (1921). *Arch. Neurol. Psychiat.*, **6,** 400.
Lattes, R. (1943). *Amer. J. Obstet. Gynec.*, **46,** 149.
Lewis, F. T., and Thyng, F. W. (1907–8). *Amer. J. Anat.*, **7,** 505.
Roth, M. (1881). *Virchows Arch.*, **86,** 371.
Stoesser, A. V. (1928). *Amer. J. Dis. Child.*, **35,** 885.
Wright, G. (1919–20). *Proc. roy. Soc. Med.*, **13,** 119.

IMPERFORATE ANUS :

SOME OBSERVATIONS REGARDING DIAGNOSIS OF THE LEVEL OF OBSTRUCTION

BY

A. W. WILKINSON, F.R.C.S.Ed.

(From the Department of Clinical Surgery, University of Edinburgh and the Royal Hospital for Sick Children, Edinburgh)

In determining the precise method of treatment and prognosis in cases of imperforate anus much depends on the level at which the blind end of the rectum lies. Where the obstruction is membranous there is usually little difficulty in diagnosis, a bluish bulge being present where the anal opening should be or appearing there when the child cries; the treatment of this type by cruciate incision and subsequent bouginage is both simple and effective. It is more common, however, to find an obstruction at a somewhat higher level, the blind end of the rectum being just so high that the contained meconium does not show through the intervening and overlying skin tissues, or at varying levels up to the brim of the pelvis. Unless there is an associated urogenital fistula intestinal obstruction will be complete. Provided that the level of the blind end is not too high it is possible to bring down the rectum and suture it to the skin of the perineum per primam. When the rectum ends at a high level it is difficult to find the stump in the newly-born child, and attempts at primary proctoplasty are dangerous and difficult; the wiser course in such cases is to carry out colostomy only and defer the plastic operation. It is of value therefore to have accurate knowledge of the level of the blind end before deciding on the operative approach.

Wangensteen and Rice (1930) have described an ingenious method of determining the relationship of the perineal skin and the blind end of the rectum. The pelvis and abdomen are x-rayed while the child is held inverted, a metal marker being placed on the perineum. The gas in the colon rises and outlines the blind end of the rectum, the relation of which to the perineal marker may then be judged. It has been pointed out by Ladd and Gross (1941) that caution must be exercised in the interpretation of such films since the gas may not have reached the blind end of the rectum at the time of examination. They quote two cases in which at four and eight hours after birth it had reached only the terminal ileum and mid-transverse colon respectively leading them erroneously to believe that obstructions existed at these points. They stated that ' before fifteen to twenty hours of age the absence of gas in the rectum cannot be taken as evidence of intestinal or colonic obstruction. However, by the end of the first day of life an x-ray picture of the abdomen is an accurate method of determining the position of the blind rectal pouch.'

In view of this the following case appears to be of importance.

Case record

The patient was a full-term male baby 5 lb. 15½ oz. in weight (spontaneous delivery, vertex, L.O.A. labour lasting 7½ hours), well-developed and of healthy appearance except for the following features: The anus was represented by a shallow wrinkled depression about a ¼ in. in depth, no bluish membrane being present; both testicles were fully descended and lying in the scrotum the median line of which was shallowly cleft. The penis was well developed, but the prepuce could not be retracted. A fine red line ran along the median ventral surface of the penis and there were two dark purple thin-walled cysts, which appeared to contain blood, on the surface of the posterior third of the median raphe of the scrotum. A diagnosis of imperforate anus was made. X-ray examination thirty-six hours after birth in the upright and inverted positions with a perineal marker, showed no gas in rectum, the gas shadow reaching only to the level of the pelvic brim; there was considerable gas distension of the small intestine and colon, and an abnormality of the scrotum and coccyx (fig. 1, 2, 3).

At operation examination of the perineal depression showed some bulging during crying and a slight impulse was palpable. It was decided, therefore, to try needling in an attempt to locate the blind rectal pouch. A wide-bore needle was inserted, but no meconium could be aspirated; after withdrawal of the needle, however, a drop of meconium was blown out of the end of the needle. A deep cruciate incision was made into the floor of the anal depression and at a depth of half an inch meconium was encountered; about half a pint of very thick viscid meconium, under considerable tension, slowly escaped. A slight ooze of blood from the incision was readily controlled by a gauze dressing.

On the third day the proximal cyst on the scrotum ruptured and meconium escaped from the resultant fistula; a finger inserted into the anus caused a gush of meconium from the fistula. Subsequently, meconium and later faeces were passed both by the anus and the fistula, but urine was passed only from

FIG. 1.—Antero-posterior x-ray in upright position showing gross distension of intestines with gas.

FIG. 2.—Oblique x-ray in upright position to show gross gaseous distension of intestines with clear definition of caecum and ascending colon below liver and the lower limit of the pelvic colon gas lying just above the pelvic brim.

the external urinary meatus and was never contaminated by meconium or faeces. Weekly dilatation by bougies increased the size of the anal passage and the proportion of faeces passed by this route. At the age of ten weeks the child died of pneumonia.

FIG. 3.—X-ray in inverted position to show marker on perineal dimple and the summit of the gas shadow in the pelvic colon. The larger shadow of the caecum and ascending colon can be distinguished by the shadow of the lower part of the right lobe of the liver.

Comment

The meconium was so thick and viscid that it is unlikely that it could have been rapidly displaced by gas. It is by no means unusual to find such viscid meconium, and it seems that the somewhat dogmatic statement of Ladd and Gross, that gas will be present at the rectal stump after twenty-four hours, requires modification. The advantages of cruciate incision or primary proctoplasty over colostomy are sufficient to make the former desirable whenever possible. It is recommended that, even in the absence of radiological signs of gas in the rectum, blind puncture and aspiration should be carried out with a wide-bore needle, when a little of the thick meconium may be sucked into the tip of the needle, although it may be too thick to be sucked into the barrel of the syringe. The rectoperineal fistula which subsequently developed in this patient opened further forwards than usual and was associated with a partial bifid scrotum; a similar condition was found once in a series of 118 fistulae recorded by Ladd and Gross (1941).

Thanks are due to Dr. Grant Allan, radiologist to the hospital, for examining the patient and allowing the reproduction of the x-ray pictures.

REFERENCES

Ladd, W. E., and Gross, R. E. (1941). Abdominal surgery of infancy and childhood, Philadelphia, p. 166.

Wangensteen, O. M., and Rice, C. O. (1930). *Ann. Surg.*, **92,** 77.

ALLERGIC VOMITING IN AN INFANT

BY

H. S. BRODRIBB, D.M. (Oxon.)

Honorary Anaesthetist, Royal East Sussex Hospital; Temporary Captain (Graded Physician) R.A.M.C.

Food allergy is well recognized as a cause for such general reactions as asthma, eczema, or urticaria. Bray (1931) states that it is especially frequent in children, and also mentions such contact reactions as blistering of the lips, vomiting, diarrhoea, shock, and even death in hypersensitive infants. Paterson and Forest Smith (1940) discussing infantile eczema state that the allergen in the majority of cases is lactalbumin. A case is now described in which vomiting was the only obvious symptom. This fact led to a considerable delay in the diagnosis, which was mistaken for a defect of digestion.

Case history

The patient was a boy, a second child, weighing 7 lb. 13 oz. at birth. His elder sister has shown no signs of allergy of any kind. His mother was in the habit of drinking liberal quantities of milk, both before and after each of them was born. He was entirely breast fed until the age of five months, and did extremely well. No cow's milk was given in the neonatal period. If anything, he was slightly overfed, doubling his birth weight at just over four months. From five months he was given, occasionally, a few teaspoonfuls of diluted cow's milk (which had been brought to the boil and cooled) with a little cereal or a patent food. This was invariably vomited except on the first two or three occasions, when small quantities were taken. Attempts were repeated at intervals of a few weeks. Further attempts were made with diluted or citrated milk only, and the vomiting was more severe.

A detailed description may be worth recording, as it seems, now, to be significant:

No more than two ounces were taken and often much less. He then seemed tired, began to yawn, salivate, and cough. About a minute or two later, violent gastric contractions could be felt and often heard, and a straining copious vomit was produced consisting of saliva and gastric juice, and containing the small quantity of milk that had been taken. After this he was exhausted, and refusing further food, went to sleep. This was in strong contrast to the small, free-flowing vomit which occasionally occurred after a breast feed, and after which he often demanded more.

The possibility of hypersensitivity had been considered by this time, but in the absence of any other signs, such as eczema, and after discussing it with other medical friends, it was discounted as being unlikely. No redness or swelling of the lips had been noticed.

By the time he was 7½ months old, weaning from the breast appeared more urgent, and cow's milk was abandoned for ' humanized ' dried milk, which had been found to give good results in other infants. This was only tried on three occasions because the vomiting and exhaustion were more severe. On the third occasion when he was over eight months old, erythema was noticed in the folds of his neck where it had rubbed his bib, which was wet with the food. A piece of lint, moistened with the food, and on which had been sprinkled some of the dried powder, was applied to the intact skin of the forearm, and bound on for twenty minutes. An intense erythema and an urticarial wheal about ¾ inch in diameter developed. The erythema persisted for some hours. A similar patch test was done with unheated cow's milk, and this took one hour before a positive but less marked reaction was obtained.

All attempts at giving cow's milk were stopped, and the advice of Dr. C. F. Harris, Physician to the Children's Department of St. Bartholomew's Hospital, was sought. ' Almata ' was tried at his suggestion, and apart from an occasional slight vomit, without the partial collapse, feeds were taken well. At the same time mixed feeding was started rapidly, the same cereals as before, eggs, gravy, vegetables, and bread, were all retained, and obviously enjoyed. Digestion seemed quite normal, and by 9½ months, he was completely weaned from the breast. Anything containing cow's milk was still avoided.

Investigation. Attempts were now made to identify the protein acting as allergen. Cow's milk contains 3 per cent. casein, 0·5 per cent. lactalbumin, and about 0·1 per cent. lactoglobulin. The humanized dried milk used contains 0·8 per cent. casein, 0·6 per cent. lactalbumin and 0·26 per cent. lactoglobulin (about 5·1 per cent. lactalbumin and 2·25 per cent. globulin in the dried powder). Also, the humanized dried milk is dried at a temperature below 145° F. which retains as far as possible the proteins in their natural state. On the other hand, Almata contains casein, egg yolk, and wheat flour proteins, but no lactalbumin or lactoglobulin except, perhaps, minute traces.

With these facts in mind, further patch tests were done on the arms:

Agent	Duration	Result
Almata powder	2 hours	Negative
Dried pure casein (twice)..	45 min.	Negative
Pure lactalbumin	45 min.	Negative
Casein (obtained by acidification and washing of cow's milk)	15 min.	Negative
Whey (obtained from junket)	60 nim.	Erythema and faint wheal
Secway powder	30 min.	Positive but rather less so than with humanized dried milk

These results were taken to indicate that he was insensitive to casein, either dried or in the natural state. Whey gave a positive test and contains the natural lactalbumin and globulin. Secway is a preparation of whey, dried below 145° F. and it contains, in the powder, about 11 per cent. albumin and 2·5 per cent. globulin. A pure specimen of lactalbumin, soluble in water, gave a negative test. It was thought that this must have been prepared from cow's milk, though that fact could not be confirmed. Unfortunately no other pure specimens could be obtained in time.

It is stated that acidification of boiled milk may render it harmless in these cases. The probable explanation is that the protein ceases to act as an allergen, in proportion to its transfer into the coagulated state. It appears that these proteins become 'denatured' on boiling at the normal pH of milk (6·6). They are not completely coagulated, except by boiling at their isoelectric point. This is pH 4·7 for lactalbumin, and pH 5·5 for lactoglobulin (Hawk and Bergeim, 1938).

Patch tests, using the humanized dried milk, were also done at various intervals:

Age	Progress	Site	Result
8 mth ..	Original test	Arm	Intense erythema, definite wheal
9 mth. ..	Nearly weaned on to Almata	Arm	Erythema, wheal less marked
9 mth. 3 wk.	Weaned off the breast	Arm	Erythema only
9 mth. 3 wk.	Weaned off the breast	Abdomen	Erythema and slight wheal
11 mth. ..	Desensitized	Abdomen	No erythema

These tests suggest that the sensitivity was decreasing either spontaneously or because of minute traces of allergen in Almata causing slight desensitization. They demonstrated that the skin of the abdomen is more likely to give a positive test in doubtful cases.

Desensitization. Specific desensitization by mouth was carried out on the advice of Dr. Harris. This was done between the tenth and eleventh month, that is, after breast feeding had stopped. The dose of boiled milk given by mouth was doubled each day. The initial dose was 1 drop of 1 in 8 suspension of milk in water; 1 drop of whole milk was given on the fourth day, and so on, until a whole pint had been taken in one day. Since then he has continued to take unmodified boiled milk as freely as any other food, and no sign of any allergic phenomenon has occurred in the subsequent twelve months. He has also taken unboiled T.T. milk, Secway and humanized dried milk, both standard, and specially prepared for him at about 195° F. by the manufacturers.

All this seems to indicate that he is desensitized, not only to denatured protein, but to protein in the natural state.

Family history. Bray points out that the stronger the hereditary influence, the earlier the age at which symptoms of allergy will have their onset. Detailed enquiries (see diagram) show that in this case, although the parents are not affected, cases of allergy occur in the families of all four grandparents. Every attempt has been made to verify these cases, most of whom are still alive; no doubtful case has been included. It will be seen that there is a strong tendency to migraine in the family of the paternal grandfather. This was produced in every case, that can still be confirmed, by eating particular types of food, e.g., beef, eggs, milk. This effect ceased in each case at about the age of 60.

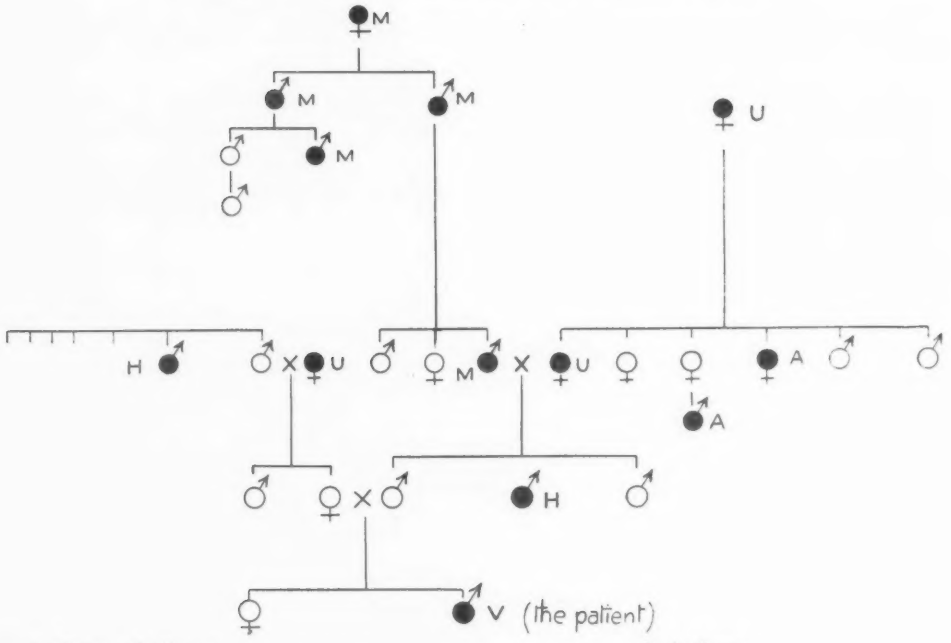
Discussion

It has been shown that the vomiting was an allergic reaction. The proof rests on (1) the result of withdrawing the cow's milk; (2) the skin tests; (3) the result of a course of desensitization. The allergen appeared to be either lactalbumin or lactoglobulin. The points against lactalbumin are: (1) the negative patch test with the specimen available, and (2) Secway gave no stronger reaction than humanized dried milk, and contains more than twice the amount of lactalbumin, but a comparable amount of globulin. The point against globulin is the small quantity of it in cow's milk. It is probably true that these proteins always occur together in the preparation of dried milk so that the exact identity of the allergen is not of practical importance. However, since it is generally agreed that lactalbumin is to blame, it is regretted that patch tests could not have been done with pure specimens of each, known to have been obtained from cow's milk. This seems to be worth doing in similar cases, where such specimens are available.

The points to be observed in the diagnosis appear to be:

(1) The type of vomiting.
(2) Family history of allergy.
(3) The skin tests.
(4) Therapeutic test by trial of appropriate food.

Skin tests may be criticized as unreliable. Bray believes, that while this may be so in adults, they are much more likely to give useful confirmatory evidence in children. They are more definite in cases of sensitivity to cow's milk if dried milk powder is used, especially if the food is prepared at a low temperature. If cow's milk or reconstituted



● Cases of allergy.
M Migraine especially after meals.
U Urticaria after certain foods.
A Asthma.
H Hay fever.
V Vomiting after cow's milk.

milk is used on the intact skin it should be applied for at least one hour.

As far as it is possible to argue from the experience of one case only, the best line of treatment appears to be: (1) weaning off the breast on to an appropriate food not containing the allergen; (2) specific desensitization by mouth. Almata was successful in this case, and lactic acid milk was not tried. If it is preferred to give it a trial, the method of preparation is described by Paterson and Forest Smith. Also it may be remembered that Cow & Gate, Ltd., make a food 'Allergilac' in which the quantity of albumin is much reduced and lactic acid is added to produce a pH of 6·0.

This report is submitted in the hope that it may assist in the early recognition of similar cases. Their accurate diagnosis and treatment is more urgent now when there is so much to discourage prolonged breast feeding. It is felt that although these cases are not rare, insufficient attention has been drawn to their occurrence, and especially to the fact that vomiting may be the only obvious symptom.

Summary.

(1) A case of an infant, allergic to cow's milk is described.

(2) The only symptom was vomiting, and this confused the diagnosis with that of defective digestion.

(3) The allergen was lactalbumin or lactoglobulin.

(4) Weaning was successful on to a food which omitted these proteins.

(5) Specific desensitization by mouth was completely effective.

Thanks are due to Dr. C. F. Harris, Physician to the Children's Department, St. Bartholomew's Hospital, for his advice on the treatment of this case, and his criticism of this report, to Keen, Robinson & Co., Ltd., makers of Almata, for their information and samples of casein and lactalbumin, and also to Trufood, Ltd., for their information and for preparing a special sample of their food.

References

Bray, G. W. (1931). *Recent advances in allergy*, Lond., 90, 343, 347, 350.

Harris, C. F. (1943). Private communication.

Hawk, P. B., and Bergeim, O. (1938). *Practical physiological chemistry*, Lond., eleventh ed., 164, 199.

Paterson, D., and Forest Smith, J. (1940). *Modern methods of feeding in infancy and childhood*, Lond., seventh ed., 78, 149.

TWO CASES OF PULMONARY ACTINOMYCOSIS

BY

ARTHUR G. WATKINS, M.D., F.R.C.P.

Physician in Children's Diseases, Cardiff Royal Infirmary and Llandough Hospital

Actinomycotic infection is rare in the lung and particularly so in children. Ellis (1935), who reviewed the literature and added five more cases, describes only one case in 11,500 autopsies at the Hospital for Sick Children, Great Ormond Street, London. It is therefore thought to be worth while reporting two cases seen recently in view of their clinical picture and recovery with sulphonamide therapy in heroic doses.

Case 1. On December 17, 1942, Peter D. was admitted to Llandough Hospital. He was a boy of two years and nine months who apart from measles and whooping cough had been well until three months before admission when he had an illness diagnosed as pneumonia and was kept in bed for fourteen days. After three weeks he was apparently well. A week before admission to hospital he started coughing and became feverish and off his food. Examination of the chest showed complete dullness at the left base of the lung with distant tubular breath sounds but without displacement of the cardiac impulse. X-ray showed a complete opacity of the whole of the left chest with a slight shift to the right of the mediastinum. A diagnosis of empyema was made and the chest explored. Thick greenish pus was obtained with a deposit of one-eighth of its total volume on standing for twelve hours. Mr. D. B. Foster was asked to deal with the case surgically and he proposed to do a rib resection with a closed drainage. During anaesthesia the child collapsed with a poor pulse and it was decided, fortunately in view of subsequent findings, to drain by a simple intercostal tube. The following day the Pathology Department reported 'the aspirated fluid contained numerous pus cells with gram positive cocci and a small number of gram positive branching filaments indistinguishable from streptothrix actinomycosis.' On anaerobic culture there was a pure growth of actinomyces bovis.

For the next four weeks there was considerable drainage of pus and the boy's temperature varied between normal and 100° F. with an occasional spike to 103°. His general condition improved, but there was still some dullness at the left base and an x-ray showed a fair sized opacity with a small pneumothorax above it. The clinical signs gradually improved and the discharge lessened and for three months he remained apyrexial except for one short spell of fever due to a haemolytic streptococcal throat infection.

Five months after admission his wound broke down and started discharging pus which again contained actinomyces. A drainage tube was re-inserted under anaesthesia, but after a month this was removed and since July, 1943, there has been no discharge with no abnormal clinical signs in the chest.

When the condition was diagnosed as actinomycosis he was given Lugol's iodine 3 minims t.d.s. and this was continued throughout. In addition sulphonamide therapy was started. This was given in short spells of a week's duration of 1½ gm. initially and continuing with 1 gm. four-hourly by day. In all 120 gm. of sulphapyridine were given and finally, after the wound broke down, he was given 5 gm. daily of sulphadiazine continuously for thirty-four days. He thus had a total of 290 gm. over a period of six months. Throughout, a careful check was kept on his blood count, but at no time did the white cells fall below 10,000 with a maximum of 17,000 per c.mm. The polymorphonuclears remained above 50 per cent. He took both drugs without any symptomatic trouble and the urine was kept alkaline with potassium citrate and sodium bicarbonate.

On discharge he was looking well and had gained weight. There were no detectable abnormal signs in his chest; x-ray showed some enlargement of the left hilar gland shadow, but the lung fields were clear. He was seen three months and again six months after going home and his progress had been well maintained.

Case 2, On September 1, 1943, Jimmy M., aged eighteen months was admitted to Cardiff Royal Infirmary. He had been ill with a cough for three weeks and had collapsed on the day of admission. There had been some cough since bronchopneumonia eleven months previously. On admission the child was ill with distressed breathing and some recession of the ribs and cyanosis. His temperature was 100° F., pulse rate 180, and respiratory rate 58. There were a few scattered rhonchi on both sides of the chest and an impaired percussion note at the right base. X-ray showed collapse of the right lower lobe with a pneumothorax. His condition gradually improved after placing him in an oxygen tent and five days later there was increased dullness at the right base with hyper-resonance above and tubular breath sounds. A diagnosis of a ruptured lung abscess with a pneumothorax was made. A blood count showed a leucocytosis of 13,500 per c.mm. with 62 per cent. lymphocytes and 27 per cent. polymorphonuclears.

Three weeks after admission the x-ray showed a hydropneumothorax at the right side with media-

stinal displacement. The child's general condition was slowly improving though he still had a cough. The cough was not typical of whooping cough, though the blood film had suggested this possibility and cough plates were negative for pertussis. A Mantoux tuberculin reaction 1:1000 was negative. A week later, in view of the signs of fluid at the right base, it was decided to aspirate the chest and at the second attempt about 2 c.c. of thick pus was withdrawn. This contained numerous pus cells, and the film showed threads morphologically indistinguishable from actinomyces.

In view of the experience with the first case it was decided to treat this one on similar lines except that this time continuous chemotherapy was indicated along with alkalinization of the urine and Lugol's iodine as before. He was therefore given 5 gm. of sulphadiazine daily, and this was continued for five weeks totalling 175 gm. Owing to difficulties in obtaining this preparation treatment was changed to sulphamezathine in similar dosage for a further 70 gm. and then he was given sulphathiazole up to another 70 gm., a total of 315 gm. in all. These changes were dictated by the supplies of these drugs available. Blood counts were repeated at weekly intervals and the white cells remained high, usually around 16,000, but ranging from 14,000 to 30,000 per c.mm. There was a variable proportion of lymphocytes and polymorphonuclears which was difficult to interpret; one week the lymphocytes would be 70 per cent. with 25 per cent. polymorphonuclears and the next the position would be reversed. This went on throughout with the lymphocytes usually predominant.

During the whole of this period the patient had remained apyrexial, but there were still scattered crepitations in his lung fields on both sides, but mainly on the right. X-ray showed complete re-expansion of the right lobe with disappearance of the fluid. Aspiration was tried again, but nothing obtained. Attempts to find the actinomyces again by stomach wash-out, post-nasal swabs and in the faeces were all unsuccessful.

Treatment stopped for a fortnight and he remained without fever, but he began to lose a little weight and his cough became worse. X-ray showed some small diffuse shadows in both lungs, the sort of film seen with a bronchopneumonia. Although the organism could not be recovered it was felt that in view of the persistence of radiological signs and the cough it was correct to continue with therapy. He was accordingly re-started with sulphathiazole at the same dosage of 5 gm. daily, and this was kept up for five weeks and two days. This gave him a total intake of various kinds of sulphonamide of 500 gm. His symptoms again improved with treatment and the x-ray was clearer. His general condition was very much better and he had gained 8 lb. in seven months.

He was sent home four weeks after all therapy had ceased, eating well and continuing to gain weight. There were still a few crepitations in his chest from time to time and the x-ray picture remained unchanged. He has been seen since and remains clinically well with only a slight cough.

Discussion

In Ellis's review he found no child with actinomycosis of the lung who had recovered, but he himself recorded a child who was well 2½ years after the onset of his illness. It is therefore early days to be too optimistic about these two cases, although it is difficult to avoid attributing their present good health to chemotherapy.

There is an increasing literature on the treatment of actinomycosis with the sulphonamide drugs but no reference has been found of its use in pulmonary involvement in children. It is in accord with experience with these drugs that agranulocytic reactions, if they are going to take place, occur within a short time of their initial use. Nevertheless, it is obviously important to keep a close watch on both the urine and blood. In judging the dosage in these two cases great difficulty was experienced in knowing if and when the infection had ceased. It was thought wiser therefore to continue its use and be guided by clinical signs as it was impossible to recover the organism after the first occasion. It may well be that the drugs were of no value after a certain stage, but as there was no evidence of intolerance or toxicity it seemed wise to continue them.

Reference

Ellis, R. W. B. (1935). *Arch. Dis. Childh.*, **10**, 1.

CORRECTION

THE FATE OF PREMATURE BABIES IN WARWICKSHIRE

Dr. C. Fraser Brockington has written to apologize for certain errors in the figures given in the table on p. 94 of his contribution in the June issue under the above title. The correct version of the table is as follows:—

PREMATURE BIRTHS IN WARWICKSHIRE, 1943

Total births .. 8650 No. premature .. 329 Percentage premature .. 3·8

Weight group, lb.	No. of premature births									No. dying (days of survival)														Over	No. surviving							Total	Percentage survival
	Born alive							Total	Born dead	First week							Second week																	
	A_1	A_2	A_3	B_1	B_2	C_1	C_2			1	2	3	4	5	6	7	8	9	10	11	12	13	14		A_1	A_2	A_3	B_1	B_2	C_1	C_2		
5–5½ ..	2	4	16	9	12	28	42	113	10	3	2	1				1		1						1	1	3	14	8	12	26	40	104	92·2
4½–5 ..	1	4	12	4	8	9	24	62	7	5	2										1			1	1	3	7	3	8	8	23	53	85·5
4–4½ ..	1	3	12	3	11	13	19	62	6	5	1		1	2		1										2	10	2	9	11	18	52	83·9
3½–4 ..	6	2	11	1	3	7	3	33	8	4			1					1	1					1	6	1	7	1	1	6	3	25	75·9
3–3½ ..	1		8	1	2	9	5	26	4	6	4	1				2	1				3		1		1		3				4	8	30·8
2½–3 ..		1	2	2		7	1	13	3	7	1	1	1											1		1					1	2	15·4
2–2½ ..	1		2			2	4	9	3	4	2													1	1						1	2	22·2
1½–2 ..	1		2	1		2	1	7	3	4	1	1			1																	} 9·0
1–1½ ..		2				2		4	2	2	1															1					1	
TOTAL ..	13	16	65	21	36	79	99	329	46	40	14	4	3	2	1	4	1	2	1	0	4	0	1	5	10	11	41	14	30	51	90	247	75·4
										82																							

A_1 Attended by an independent midwife.
A_2 Attended by a county council midwife.
A_3 Attended by a district nursing association midwife.
B_1 Born in a nursing home.
B_2 Born in a maternity home.
C_1 Born in a municipal hospital.
C_2 Born in a voluntary hospital.

He sends the following comments:—

The figure for the municipal hospitals has been altered; total of premature babies reading 79 in place of 61; with 51 surviving instead of 39. The survival rate is 65 instead of 64 (D–C in the script $=25\pm6{\cdot}1$).

This makes no difference to the inferences to be drawn, but it causes a number of minor alterations in the table and the script:—

1. The numbers and times of those dying are changed:

82 died, 54 in the first 48 hours, i.e. 67 per cent., and 83 per cent. in the first week.

Of those over 3½ lb. 22 out of 36 (60 per cent.) died in the first 48 hours.

Of those under 3½ lb. 32 out of 46 (70 per cent.) died in the first 48 hours.

The percentage dying in the first 48 hours is thus not 'higher' in the over 3½ pounders as stated in the script, but 'nearly as high'

2. The percentage survivals are altered throughout, but not appreciably. Also one baby survived under 2 lb. out of 16 instead of 15.

3. The number of prematures reads 329 and the percentage of prematures is raised from 3·6 to 3·8.